SEARCH NOTES


```
=> fil reg; d ide 1-4
FILE 'REGISTRY' ENTERED AT 12:01:36 ON 10 MAY 2005
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:     9 MAY 2005  HIGHEST RN 850130-09-5
DICTIONARY FILE UPDATES:    9 MAY 2005  HIGHEST RN 850130-09-5

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

**********************************************************************
*                                                                    *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,    *
* effective March 20, 2005.  A new display format, IDERL, is now     *
* available and contains the CA role and document type information.  *
*                                                                    *
**********************************************************************

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html


L5   ANSWER 1 OF 4  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   32511-63-0  REGISTRY
ED   Entered STN:  16 Nov 1984
CN   9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, (3β,5Z,7E)- (9CI)
     (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   9,10-Secocholesta-5,7,10(19)-triene-1,3β,25-triol (8CI)
OTHER NAMES:
CN   1,25-Dihydroxycholecalciferol
CN   1,25-Dihydroxyvitamin D3
FS   STEREOSEARCH
DR   31448-33-6
MF   C27 H44 O3
LC   STN Files:   ADISNEWS, AGRICOLA, BEILSTEIN*, BIOBUSINESS, BIOSIS,
       BIOTECHNO, CA, CAPLUS, CHEMINFORMRX, CIN, EMBASE, IFICDB, IFIPAT,
       IFIUDB, PROMT, SPECINFO, TOXCENTER, USPAT2, USPATFULL
         (*File contains numerically searchable property data)

Absolute stereochemistry.
Double bond geometry as shown.
```
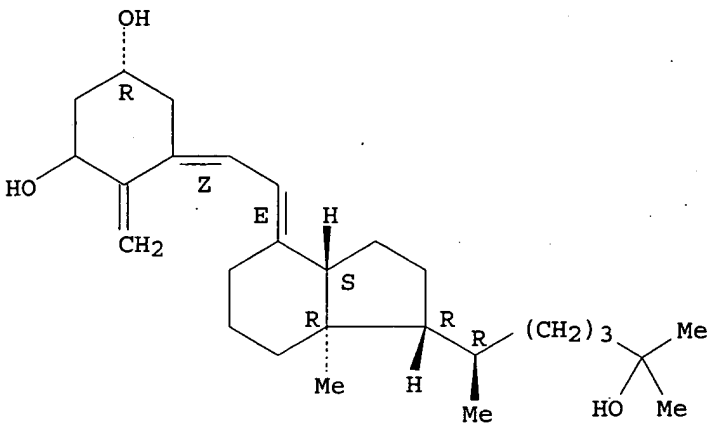
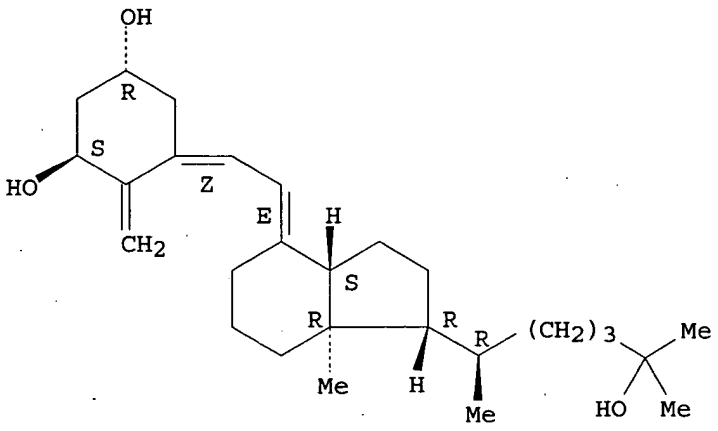



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1006 REFERENCES IN FILE CA (1907 TO DATE)
14 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1008 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5 ANSWER 2 OF 4 REGISTRY COPYRIGHT 2005 ACS on STN
RN 32222-06-3 REGISTRY
ED Entered STN: 16 Nov 1984
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, (1α,3β,5Z,7E)-(9CI) (CA INDEX NAME)
OTHER NAMES:
CN (3β,5Z,7E)-9,10-Secocholesta-5,7,10(19)-trienetriol
CN **1,25-Dihydroxycholecalciferol**
CN 1,25-Dihydroxyvitamin D
CN **1,25-Dihydroxyvitamin D3**
CN 1α,25-(OH)2D3
CN 1α,25-Dihydroxycholecalciferol
CN 1α,25-Dihydroxyvitamin D3
CN Calcijex
CN Calcitriol
CN Dihydroxyvitamin D3
CN Ro 21-5535
CN Rocaltrol
CN Silkis
CN Soltriol
CN Topitriol
CN Toptriol
FS STEREOSEARCH
DR 125338-24-1, 69878-52-0
MF C27 H44 O3
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DIOGENES, DRUGU, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, NAPRALERT, NIOSHTIC, PHAR, PROMT, PS, RTECS*, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.



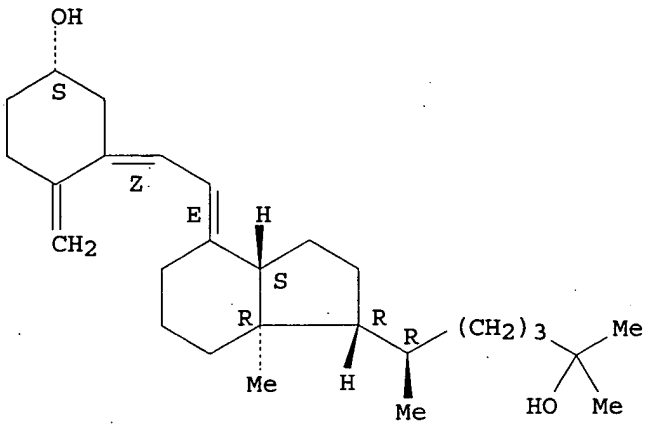
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

10353 REFERENCES IN FILE CA (1907 TO DATE)
308 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
10362 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5 ANSWER 3 OF 4 REGISTRY COPYRIGHT 2005 ACS on STN
RN 19356-17-3 REGISTRY
ED Entered STN: 16 Nov 1984
CN 9,10-Secocholesta-5,7,10(19)-triene-3,25-diol, (3β,5Z,7E)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 9,10-Secocholesta-5,7,10(19)-triene-3β,25-diol (8CI)
OTHER NAMES:
CN 25-HCC
CN 25-Hydroxycholecalciferol
CN 25-Hydroxyvitamin D
CN **25-Hydroxyvitamin D3**
CN 5,6-cis-25-Hydroxyvitamin D3
CN Calcidiol
CN Calcifediol
CN Calderol
CN Cholecalciferol, 25-hydroxy-
CN Dedrogyl
CN Didrogyl
CN Hidroferol
CN Ro 8-8892
CN U 32070E
FS STEREOSEARCH
DR 25631-40-7
MF C27 H44 O2
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PROMT, PS, SPECINFO, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO

(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.
Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3032 REFERENCES IN FILE CA (1907 TO DATE)
44 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
3032 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5 ANSWER 4 OF 4 REGISTRY COPYRIGHT 2005 ACS on STN
RN 1406-16-2 REGISTRY
ED Entered STN: 16 Nov 1984
CN **Vitamin D (8CI, 9CI)** (CA INDEX NAME)
MF Unspecified
CI COM, MAN
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMLIST, CIN, CSNB, DDFU, DIOGENES, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, NAPRALERT, NIOSHTIC, PIRA, PROMT, RTECS*, TOXCENTER, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
11392 REFERENCES IN FILE CA (1907 TO DATE)
905 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
11403 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> □

=> fil medl
FILE 'MEDLINE' ENTERED AT 12:08:20 ON 10 MAY 2005

FILE LAST UPDATED: 6 MAY 2005 (20050506/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

The MEDLINE reload for 2005 is now available. For details enter HELP

RLOAD at an arrow promt (=>). See also:

http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> e epithelial cells+nt/ct
E1       39771   -->   Epithelial Cells/CT
E2      158805   MN    A11.436./CT
E3        1009    NT1   Ameloblasts/CT
E4       19195    NT1   CHO Cells/CT
E5        3023    NT1   Caco-2 Cells/CT
E6          38    NT1   Chief Cells, Gastric/CT
E7         986    NT1   Chromatophores/CT
E8         666     NT2   Melanophores/CT
E9         339      NT3   Melanosomes/CT
E10      11608    NT1   Dendritic Cells/CT
E11       3977     NT2   Langerhans Cells/CT
E12        996    NT1   Enterochromaffin Cells/CT
E13        132    NT1   Enterochromaffin-like Cells/CT
E14        708    NT1   Enterocytes/CT
E15        440    NT1   Goblet Cells/CT
E16       5088    NT1   Granulosa Cells/CT
E17       1422    NT1   HT29 Cells/CT
E18      39445    NT1   Hela Cells/CT
E19       1194     NT2   KB Cells/CT
E20       6226    NT1   Hepatocytes/CT
E21      10187    NT1   Keratinocytes/CT
E22        714    NT1   LLC-PK1 Cells/CT
E23         97    NT1   Labyrinth Supporting Cells/CT
E24       5717    NT1   Melanocytes/CT
E25        339     NT2   Melanosomes/CT
E26        118    NT1   Merkel Cells/CT
E27          3    NT1   Neuroepithelial Cells/CT
E28       3746     NT2   Hair Cells/CT
E29        893      NT3   Hair Cells, Inner/CT
E30        978      NT3   Hair Cells, Outer/CT
E31        315      NT3   Hair Cells, Vestibular/CT
E32          1     NT2   Neuroepithelial Bodies/CT
E33        108    NT1   Paneth Cells/CT
E34       1559    NT1   Parietal Cells, Gastric/CT
E35       4451    NT1   Sertoli Cells/CT
E36       6652    NT1   Vero Cells/CT
********** END **********

=> e vitamin d+nt/ct
E1        9812   -->   Vitamin D/CT
E2       26411   MN    D11.786.763./CT
E3        3582    NT1   Cholecalciferol/CT
E4        3271     NT2   Hydroxycholecalciferols/CT
E5        1969      NT3   Calcifediol/CT
E6        9743      NT3   Calcitriol/CT
E7        1958      NT3   Dihydroxycholecalciferols/CT
```

```
E8          694        NT4   24,25-Dihydroxyvitamin D 3/CT
E9         9743        NT4   Calcitriol/CT
E10         473     NT1   Dihydrotachysterol/CT
E11        1542     NT1   Ergocalciferols/CT
E12         347      NT2   25-Hydroxyvitamin D 2/CT
E13        1098     NT1   Ergosterol/CT
********** END **********

=> e apoptosis+nt/ct
E1        71056    -->   Apoptosis/CT
E2        72805    MN    G4.335.139.160./CT
E3          143     NT1   Anoikis/CT
E4         7215     NT1   DNA Fragmentation/CT
********** END **********
```

```
=> □

=> fil capl; d que l14; d que l45
FILE 'CAPLUS' ENTERED AT 12:53:30 ON 10 MAY 2005
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FILE COVERS 1907 - 10 May 2005  VOL 142 ISS 20
FILE LAST UPDATED: 9 May 2005  (20050509/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.
'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE


L1             1 SEA FILE=REGISTRY ABB=ON  "VITAMIN D"/CN
L2             1 SEA FILE=REGISTRY ABB=ON  "25-HYDROXYVITAMIN D3"/CN
L3             2 SEA FILE=REGISTRY ABB=ON  "1,25-DIHYDROXYVITAMIN D3"/CN
L4             2 SEA FILE=REGISTRY ABB=ON  "1,25-DIHYDROXYCHOLECALCIFEROL"/CN
L5             4 SEA FILE=REGISTRY ABB=ON  (L1 OR L2 OR L3 OR L4)
L7         22302 SEA FILE=CAPLUS ABB=ON  L5
L11        73956 SEA FILE=CAPLUS ABB=ON  APOPTOSIS/CT
L12        21981 SEA FILE=CAPLUS ABB=ON  EPITHELIUM/CT
L13         4865 SEA FILE=CAPLUS ABB=ON  L7(L)(BAC OR PAC OR PKT OR DMA OR
                 THU)/RL
L14            4 SEA FILE=CAPLUS ABB=ON  L13 AND L11 AND L12

Roles
BAC - biological activity
PAC - pharmacologic activity
PKT - pharmacokinetics
DMA - drug mechanism of action
THU - therapeutic use

L1             1 SEA FILE=REGISTRY ABB=ON  "VITAMIN D"/CN
L2             1 SEA FILE=REGISTRY ABB=ON  "25-HYDROXYVITAMIN D3"/CN
L3             2 SEA FILE=REGISTRY ABB=ON  "1,25-DIHYDROXYVITAMIN D3"/CN
L4             2 SEA FILE=REGISTRY ABB=ON  "1,25-DIHYDROXYCHOLECALCIFEROL"/CN
L5             4 SEA FILE=REGISTRY ABB=ON  (L1 OR L2 OR L3 OR L4)
L7         22302 SEA FILE=CAPLUS ABB=ON  L5
L9         84060 SEA FILE=CAPLUS ABB=ON  OVAR?/OBI
L11        73956 SEA FILE=CAPLUS ABB=ON  APOPTOSIS/CT
L13         4865 SEA FILE=CAPLUS ABB=ON  L7(L)(BAC OR PAC OR PKT OR DMA OR
                 THU)/RL
L43           10 SEA FILE=CAPLUS ABB=ON  L9 AND L11 AND L13
L45            4 SEA FILE=CAPLUS ABB=ON  L43 AND (SUPPRESS? OR PREVENT?)/TI


=> s l14 or l45
```

```
L85          7 L14 OR L45

=> fil cancer medl; d que l55; d que l57

FILE 'CANCERLIT' ENTERED AT 12:53:32 ON 10 MAY 2005

FILE 'MEDLINE' ENTERED AT 12:53:32 ON 10 MAY 2005


L16        29987 SEA VITAMIN D+NT/CT
L17       103421 SEA APOPTOSIS+NT/CT
L18       185782 SEA EPITHELIAL CELLS+NT/CT
L46       201135 SEA EPITHELIUM+NT/CT
L49        60745 SEA (L18 OR L46)(L) DE/CT
L51        18069 SEA L16(L)(PD OR AD OR TU OR PK)/CT
L55           22 SEA L51/MAJ AND L17 AND L49



L16        29987 SEA VITAMIN D+NT/CT
L17       103421 SEA APOPTOSIS+NT/CT
L47        61044 SEA OVARY+NT/CT
L51        18069 SEA L16(L)(PD OR AD OR TU OR PK)/CT
L57            0 SEA L51 AND L17 AND L47


=> fil embase; d que l31; d que l35; d que l42

FILE 'EMBASE' ENTERED AT 12:53:32 ON 10 MAY 2005
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 FILE COVERS 1974 TO 5 May 2005 (20050505/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


L23        34864 SEA FILE=EMBASE ABB=ON  VITAMIN D+NT/CT
L24        81091 SEA FILE=EMBASE ABB=ON  APOPTOSIS/CT
L26        49175 SEA FILE=EMBASE ABB=ON  OVARY+NT/CT
L28        11662 SEA FILE=EMBASE ABB=ON  L23(L)(PD OR PK OR AD OR DO OR DT)/CT
L31            1 SEA FILE=EMBASE ABB=ON  L28 AND L24 AND L26



L23        34864 SEA FILE=EMBASE ABB=ON  VITAMIN D+NT/CT
L24        81091 SEA FILE=EMBASE ABB=ON  APOPTOSIS/CT
L25       139809 SEA FILE=EMBASE ABB=ON  EPITHELIUM CELL+NT/CT
L28        11662 SEA FILE=EMBASE ABB=ON  L23(L)(PD OR PK OR AD OR DO OR DT)/CT
L32       133976 SEA FILE=EMBASE ABB=ON  EPITHELIUM+NT/CT
L33           16 SEA FILE=EMBASE ABB=ON  L28/MAJ AND L24 AND (L25 OR L32)
L34      1280287 SEA FILE=EMBASE ABB=ON  NEOPLASM+NT/CT
L35            7 SEA FILE=EMBASE ABB=ON  L33 NOT L34



L23        34864 SEA FILE=EMBASE ABB=ON  VITAMIN D+NT/CT
L24        81091 SEA FILE=EMBASE ABB=ON  APOPTOSIS/CT
```

Subheadings
DE - drug effects
PD - pharmacology
AD - administration & dosage
TU - therapeutic use
PK - pharmacokinetics

PD - pharmacology
PK - pharmacokinetics
AD - administration
DO - dosage
DT - drug therapy

```
L25      139809 SEA FILE=EMBASE ABB=ON  EPITHELIUM CELL+NT/CT
L28       11662 SEA FILE=EMBASE ABB=ON  L23(L)(PD OR PK OR AD OR DO OR DT)/CT
L32      133976 SEA FILE=EMBASE ABB=ON  EPITHELIUM+NT/CT
L33          16 SEA FILE=EMBASE ABB=ON  L28/MAJ AND L24 AND (L25 OR L32)
L39        7163 SEA FILE=EMBASE ABB=ON  CHEMOPROPHYLAXIS/CT
L40      142668 SEA FILE=EMBASE ABB=ON  DRUG EFFECT/CT
L41       16368 SEA FILE=EMBASE ABB=ON  CANCER INHIBITION/CT
L42           6 SEA FILE=EMBASE ABB=ON  L33 AND (L39 OR L40 OR L41)


=> s l31 or l35 or l42

L86          12 L31 OR L35 OR L42

=> fil drugu; d que l70

FILE 'DRUGU' ENTERED AT 12:53:34 ON 10 MAY 2005
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FILE LAST UPDATED: 9 MAY 2005        <20050509/UP>
>>>  DERWENT DRUG FILE (SUBSCRIBER)  <<<

>>>  FILE COVERS 1983 TO DATE  <<<
>>>  THESAURUS AVAILABLE IN /CT  <<<


L1             1 SEA FILE=REGISTRY ABB=ON  "VITAMIN D"/CN
L2             1 SEA FILE=REGISTRY ABB=ON  "25-HYDROXYVITAMIN D3"/CN
L3             2 SEA FILE=REGISTRY ABB=ON  "1,25-DIHYDROXYVITAMIN D3"/CN
L4             2 SEA FILE=REGISTRY ABB=ON  "1,25-DIHYDROXYCHOLECALCIFEROL"/CN
L5             4 SEA FILE=REGISTRY ABB=ON  (L1 OR L2 OR L3 OR L4)
L58         6203 SEA FILE=DRUGU ABB=ON  VITAMINS-D+NT/CT
L59        12638 SEA FILE=DRUGU ABB=ON  APOPTOSIS/CT
L60          587 SEA FILE=DRUGU ABB=ON  EPITHELIAL/CT OR EPITHELIAL-CELL/CT
L61         4742 SEA FILE=DRUGU ABB=ON  EPITHELIUM/CT
L63        25360 SEA FILE=DRUGU ABB=ON  OVAR?
L64         8515 SEA FILE=DRUGU ABB=ON  APOPTOSIS-INDUCER/CT
L67        30748 SEA FILE=DRUGU ABB=ON  VITAMINS/CC
L69         1406 SEA FILE=DRUGU ABB=ON  L5
L70            3 SEA FILE=DRUGU ABB=ON  (L58 OR L69) AND (L59 OR L64) AND
                  (((L60 OR L61)) OR (L63 AND L67))


=> fil PASCAL, BIOTECHNO, BIOSIS, IPA, CONFSCI, DISSABS, TOXCENTER, WPIDS

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=> d que l80; d que l82

L1             1 SEA FILE=REGISTRY ABB=ON  "VITAMIN D"/CN
L2             1 SEA FILE=REGISTRY ABB=ON  "25-HYDROXYVITAMIN D3"/CN
L3             2 SEA FILE=REGISTRY ABB=ON  "1,25-DIHYDROXYVITAMIN D3"/CN
L4             2 SEA FILE=REGISTRY ABB=ON  "1,25-DIHYDROXYCHOLECALCIFEROL"/CN
L5             4 SEA FILE=REGISTRY ABB=ON  (L1 OR L2 OR L3 OR L4)
L71        83087 SEA (HYDROXYVITAMIN OR DIHYDROXYVITAMIN OR VITAMIN)(W)(D OR D2
                 OR D3) OR CHOLECALCIFEROL# OR DIHYDROTACHYSTEROL# OR ERGOCALCIF
                 EROL# OR ERGOSTEROL#
L72        13741 SEA HYDROXYCHOLECALCIFEROL# OR CALCIFEDIOL# OR CALCITRIOL#
L73          330 SEA (CHOLE OR ERGO)(W) CALCIFEROL# OR (DIHYDRO OR DI HYDRO)(W)(
                 TACHYSTEROL# OR TACHY STEROL#)
L74        41391 SEA L5
L75       554854 SEA EPITHELI?
L76       294894 SEA APOPTO?
L77       175236 SEA CELL?(3A) DEATH
L78       362365 SEA OVAR?
L79          145 SEA (L71 OR L72 OR L73 OR L74) AND L75 AND (L76 OR L77)
L80           13 SEA L79 AND L78



L1             1 SEA FILE=REGISTRY ABB=ON  "VITAMIN D"/CN
L2             1 SEA FILE=REGISTRY ABB=ON  "25-HYDROXYVITAMIN D3"/CN
L3             2 SEA FILE=REGISTRY ABB=ON  "1,25-DIHYDROXYVITAMIN D3"/CN
L4             2 SEA FILE=REGISTRY ABB=ON  "1,25-DIHYDROXYCHOLECALCIFEROL"/CN
L5             4 SEA FILE=REGISTRY ABB=ON  (L1 OR L2 OR L3 OR L4)
L71        83087 SEA (HYDROXYVITAMIN OR DIHYDROXYVITAMIN OR VITAMIN)(W)(D OR D2
                 OR D3) OR CHOLECALCIFEROL# OR DIHYDROTACHYSTEROL# OR ERGOCALCIF
                 EROL# OR ERGOSTEROL#
L72        13741 SEA HYDROXYCHOLECALCIFEROL# OR CALCIFEDIOL# OR CALCITRIOL#
L73          330 SEA (CHOLE OR ERGO)(W) CALCIFEROL# OR (DIHYDRO OR DI HYDRO)(W)(
                 TACHYSTEROL# OR TACHY STEROL#)
L74        41391 SEA L5
L75       554854 SEA EPITHELI?
L76       294894 SEA APOPTO?
L77       175236 SEA CELL?(3A) DEATH
L79          145 SEA (L71 OR L72 OR L73 OR L74) AND L75 AND (L76 OR L77)
L81        38204 SEA CHEMOPROPHYL? OR CHEMOPREVENT? OR CHEMO(W)(PROPHYL? OR
                 PREVENT?)
L82           28 SEA L79 AND L81


=> s l80 or l82

L87           41 L80 OR L82
```

```
=> => dup rem l55,l70,l85,l86,l87
FILE 'CANCERLIT' ENTERED AT 12:55:37 ON 10 MAY 2005

FILE 'MEDLINE' ENTERED AT 12:55:37 ON 10 MAY 2005

FILE 'DRUGU' ENTERED AT 12:55:37 ON 10 MAY 2005
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PROCESSING COMPLETED FOR L86
PROCESSING COMPLETED FOR L87
L88           49 DUP REM L55 L70 L85 L86 L87 (36 DUPLICATES REMOVED)
                 ANSWERS '1-7' FROM FILE CANCERLIT
                 ANSWERS '8-15' FROM FILE MEDLINE
                 ANSWERS '16-18' FROM FILE DRUGU
                 ANSWERS '19-24' FROM FILE CAPLUS
                 ANSWERS '25-29' FROM FILE EMBASE
                 ANSWERS '30-36' FROM FILE PASCAL
                 ANSWER '37' FROM FILE BIOTECHNO
                 ANSWERS '38-43' FROM FILE BIOSIS
                 ANSWERS '44-45' FROM FILE DISSABS
                 ANSWERS '46-48' FROM FILE TOXCENTER
                 ANSWER '49' FROM FILE WPIDS

=> d iall 1-18; d ibib ed abs hitrn 19-24; d iall 25-49; fil hom

L88  ANSWER 1 OF 49  CANCERLIT on STN                    DUPLICATE 12
ACCESSION NUMBER:    2002165192     CANCERLIT
DOCUMENT NUMBER:     22067471   PubMed ID: 12072382
```

TITLE: Antiproliferative effects of 1alpha,25-dihydroxyvitamin D(3) and vitamin D analogs on tumor-derived endothelial cells.

AUTHOR: Bernardi Ronald J; Johnson Candace S; Modzelewski Ruth A; Trump Donald L

CORPORATE SOURCE: Department of Pharmacology, University of Pittsburgh Cancer Institute, University of Pittsburgh, Pennsylvania 15213, USA.

CONTRACT NUMBER: CA-67267 (NCI)
CA-85142 (NCI)

SOURCE: ENDOCRINOLOGY, (2002 Jul) 143 (7) 2508-14.
Journal code: 0375040. ISSN: 0013-7227.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: MEDLINE; Abridged Index Medicus Journals; Priority Journals

OTHER SOURCE: MEDLINE 2002329416

ENTRY MONTH: 200207

ENTRY DATE: Entered STN: 20020819
Last Updated on STN: 20020819

ABSTRACT:
Although there is abundant evidence that 1alpha,25-dihydroxyvitamin D(3) [1,25-(OH)(2)D(3)] inhibits the growth of several cancer cell types, inhibition of angiogenesis may also play a role in mediating the antitumor effects of 1,25-(OH)(2)D(3.) We examined the ability of 1,25-(OH)(2)D(3) to inhibit the growth of tumor-derived endothelial cells (TDECs) and normal endothelial cells and to modulate angiogenic signaling. 1,25-(OH)(2)D(3) inhibited the growth of TDECs from two tumor models at nanomolar concentrations, but was less potent against normal aortic or yolk sac endothelial cells. The vitamin D analogs Ro-25-6760, EB1089, and ILX23-7553 were also potent inhibitors of TDEC proliferation. Furthermore, the combination of 1,25-(OH)(2)D(3) and dexamethasone had greater activity than either agent alone. 1,25-(OH)(2)D(3) increased vitamin D receptor and p27(Kip1) protein levels in TDECs, whereas phospho-ERK1/2 and phospho-Akt levels were reduced. These changes were not observed in normal aortic endothelial cells. In squamous cell carcinoma and radiation-induced fibrosarcoma-1 cells, 1,25-(OH)(2)D(3) treatment caused a reduction in the angiogenic signaling molecule, angiopoietin-2. In conclusion, 1,25-(OH)(2)D(3) and its analogs directly inhibit TDEC proliferation at concentrations comparable to those required to inhibit tumor cells. Further, 1,25-(OH)(2)D(3) modulates cell cycle and survival signaling in TDECs and affects angiogenic signaling in cancer cells. Thus, our work supports the hypothesis that angiogenesis inhibition plays a role in the antitumor effects of 1,25-(OH)(2)D(3).

CONTROLLED TERM: Check Tags: Animal; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
*Angiogenesis Inhibitors: PD, pharmacology
Angiotensin II: BI, biosynthesis
Anti-Inflammatory Agents, Steroidal: PD, pharmacology
Antineoplastic Agents: AI, antagonists & inhibitors
*Antineoplastic Agents: PD, pharmacology
Apoptosis: DE, drug effects
Blotting, Western
Calcitriol: AI, antagonists & inhibitors
***Calcitriol: PD, pharmacology**
Carcinoma, Squamous Cell: ME, metabolism
Carcinoma, Squamous Cell: PA, pathology
Cell Division: DE, drug effects
Dexamethasone: PD, pharmacology
Drug Synergism

Searched by Barb O'Bryen, STIC 2-2518

Endothelium, Vascular: CY, cytology
*Endothelium, Vascular: DE, drug effects
Endothelium, Vascular: ME, metabolism
Gentian Violet
Indicators and Reagents
Mice
Neoplasms: ME, metabolism
*Neoplasms: PA, pathology
Signal Transduction: DE, drug effects
Tumor Cells, Cultured
*Vitamin D: AA, analogs & derivatives
*Vitamin D: PD, pharmacology

CAS REGISTRY NO.: 11128-99-7 (Angiotensin II); 1406-16-2 (Vitamin D); 32222-06-3 (Calcitriol); 50-02-2 (Dexamethasone); 548-62-9 (Gentian Violet)

CHEMICAL NAME: 0 (Angiogenesis Inhibitors); 0 (Anti-Inflammatory Agents, Steroidal); 0 (Antineoplastic Agents); 0 (Indicators and Reagents)

L88 ANSWER 2 OF 49 CANCERLIT on STN DUPLICATE 13

ACCESSION NUMBER: 2002094092 CANCERLIT

DOCUMENT NUMBER: 21568271 PubMed ID: 11710939

TITLE: 1Alpha,25-dihydroxyvitamin D3 protects human keratinocytes from apoptosis by the formation of sphingosine-1-phosphate.

AUTHOR: Manggau M; Kim D S; Ruwisch L; Vogler R; Korting H C; Schafer-Korting M; Kleuser B

CORPORATE SOURCE: Institut fur Pharmazie, Abteilung fur Pharmakologie, Freie Universitat Berlin, Berlin, Germany.

SOURCE: JOURNAL OF INVESTIGATIVE DERMATOLOGY, (2001 Nov) 117 (5) 1241-9.
Journal code: 0426720. ISSN: 0022-202X.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: MEDLINE; Priority Journals

OTHER SOURCE: MEDLINE 2001665927

ENTRY MONTH: 200112

ENTRY DATE: Entered STN: 20020726
Last Updated on STN: 20020726

ABSTRACT:
Owing to its ability to induce growth arrest and differentiation of keratinocytes, 1alpha,25-dihydroxyvitamin D3 and its analogs are useful for the treatment of hyperproliferative skin diseases, such as psoriasis vulgaris. It has been implicated that the 1alpha,25-dihydroxyvitamin D3-induced differentiation of keratinocytes is mediated, at least in part, by the formation of ceramides; however, ceramides have also been identified to induce apoptosis in many cells, including keratinocytes. Therefore, it was of interest to investigate the influence of 1alpha,25-dihydroxyvitamin D3 on apoptosis in keratinocytes. Most interestingly, physiological concentrations of 1alpha,25-dihydroxyvitamin D3 did not induce apoptosis in keratinocytes, despite the formation of ceramides. Moreover, 1alpha,25-dihydroxyvitamin D3 appeared cytoprotective and made keratinocytes resistant to apoptosis induced by ceramides, ultraviolet irradiation, or tumor necrosis factor-alpha. The cytoprotective effect was accompanied by the formation of the sphingolipid breakdown product sphingosine-1-phosphate, which prevented apoptosis in analogy to 1alpha,25-dihydroxyvitamin D3. The effect of 1alpha,25-dihydroxyvitamin D3 was specific as the almost inactive precursor cholecalciferol neither induced sphingosine-1-phosphate formation nor prevented cells from apoptosis. Besides this, the cytoprotective aptitude of 1alpha,25-dihydroxyvitamin D3 was completely abolished by the sphingosine kinase inhibitor N,N-

dimethylsphingosine, which blocked sphingosine-1-phosphate formation. Moreover, sphingosine-1-phosphate was able to restore the cytoprotective effect of 1alpha,25-dihydroxyvitamin D3 in the presence of N,N-dimethylsphingosine. Taken together, here we report for the first time that 1alpha,25-dihydroxyvitamin D3 protects keratinocytes from apoptosis and additionally this cytoprotection is mediated via the formation of sphingosine-1-phosphate.

CONTROLLED TERM: Check Tags: Human; Support, Non-U.S. Gov't
***Apoptosis: DE, drug effects**
***Calcitriol: PD, pharmacology**
Cell Division: DE, drug effects
Cell Survival: DE, drug effects
Cells, Cultured
Ceramides: ME, metabolism
Ceramides: PD, pharmacology
Cytoprotection
Hydroxycholecalciferols
Keratinocytes: CY, cytology
***Keratinocytes: DE, drug effects**
Keratinocytes: PA, pathology
*Keratinocytes: PH, physiology
Keratinocytes: RE, radiation effects
Necrosis
Phosphotransferases (Alcohol Group Acceptor): ME, metabolism
Proto-Oncogene Proteins c-bcl-2: ME, metabolism
*Sphingosine: AA, analogs & derivatives
*Sphingosine: BI, biosynthesis
Sphingosine: PD, pharmacology
Sphingosine: PH, physiology
Tumor Necrosis Factor: PD, pharmacology
Ultraviolet Rays

CAS REGISTRY NO.: 122314-67-4 (N,N-dimethylsphingosine); 123-78-4 (Sphingosine); 26993-30-6 (sphingosine 1-phosphate); 32222-06-3 (Calcitriol); 41294-56-8 (1-hydroxycholecalciferol)

CHEMICAL NAME: 0 (Ceramides); 0 (Hydroxycholecalciferols); 0 (Proto-Oncogene Proteins c-bcl-2); 0 (Tumor Necrosis Factor); EC 2.7.1 (Phosphotransferases (Alcohol Group Acceptor)); EC 2.7.1.- (sphingosine kinase)

L88 ANSWER 3 OF 49 CANCERLIT on STN DUPLICATE 14

ACCESSION NUMBER: 2002059217 CANCERLIT

DOCUMENT NUMBER: 21288812 PubMed ID: 11394895

TITLE: Calcipotriol inhibits autocrine phosphorylation of EGF receptor in a calcium-dependent manner, a possible mechanism for its inhibition of cell proliferation and stimulation of cell differentiation.

AUTHOR: Lee E; Jeon S H; Yi J Y; Jin Y J; Son Y S

CORPORATE SOURCE: National Research Laboratory of Tissue Engineering, Korea Cancer Center Hospital, KAERI, 215-4, Gongneung-Dong, Nowon-Gu, Seoul, 139-706, Korea.

SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (2001 Jun 8) 284 (2) 419-25.
Journal code: 0372516. ISSN: 0006-291X.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: MEDLINE; Priority Journals

OTHER SOURCE: MEDLINE 2001327658

ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20020726
Last Updated on STN: 20020726

ABSTRACT:
We report in this study that proliferation inhibition of SCC13 cells by calcipotriol was possibly mediated by its inhibitory effect on autocrine activation of EGF receptor. Based on MTT assay, PCNA staining, DAPI staining, and involucrin immunocytochemical staining, we showed that calcipotriol inhibited cell growth and stimulated differentiation but did not induce apoptosis. Western blot analysis of concanavalin-A-bound fraction demonstrated that calcipotriol specifically dephosphorylated 170- and 66-kDa polypeptides from 8 h posttreatment and complete dephosphorylation was observed at 12 h posttreatment. The 170- and 66-kDa polypeptides were confirmed as EGF receptor and Shc, respectively. Calcipotriol-mediated EGF receptor dephosphorylation required the presence of extracellular calcium. Similar kinetics of the dephosphorylation was also observed in HaCaT cells cultured in medium of high calcium concentration. By BrdU labeling, we also showed calcium dependency of calcipotriol for the inhibition of cell proliferation. Therefore, EGF receptor deactivation by calcipotriol might be a mechanism of action for the inhibition of cell proliferation and the stimulation of differentiation in SCC13 cell and HaCaT cells.

CONTROLLED TERM: Check Tags: Human; Support, Non-U.S. Gov't
*Antineoplastic Agents: PD, pharmacology
Apoptosis
*Autocrine Communication: DE, drug effects
Blotting, Western
Bromodeoxyuridine
Calcitriol: AA, analogs & derivatives
***Calcitriol: PD, pharmacology**
Calcium: ME, metabolism
*Carcinoma, Squamous Cell: ME, metabolism
*Cell Differentiation: DE, drug effects
Cell Division: DE, drug effects
Cell Line
Fluorescent Dyes
Keratinocytes: CY, cytology
Keratinocytes: DE, drug effects
Keratinocytes: ME, metabolism
Phosphorylation: DE, drug effects
Proliferating Cell Nuclear Antigen: ME, metabolism
Protein Precursors: ME, metabolism
Proteins: ME, metabolism
*Receptor, Epidermal Growth Factor: ME, metabolism
Signal Transduction: DE, drug effects
Tetrazolium Salts
Thiazoles

CAS REGISTRY NO.: 112965-21-6 (calcipotriene); 298-93-1 (thiazolyl blue); 32222-06-3 (Calcitriol); 59-14-3 (Bromodeoxyuridine); 60108-77-2 (involucrin); 7440-70-2 (Calcium)

CHEMICAL NAME: 0 (Antineoplastic Agents); 0 (Fluorescent Dyes); 0 (Proliferating Cell Nuclear Antigen); 0 (Protein Precursors); 0 (Proteins); 0 (Shc protein); 0 (Tetrazolium Salts); 0 (Thiazoles); EC 2.7.11.- (Receptor, Epidermal Growth Factor)

L88 ANSWER 4 OF 49 CANCERLIT on STN DUPLICATE 17
ACCESSION NUMBER: 2000143831 CANCERLIT
DOCUMENT NUMBER: 20143831 PubMed ID: 10679076

TITLE: 1 Alpha,25-dihydroxyvitamin D3 inhibits differentiation, maturation, activation, and survival of dendritic cells leading to impaired alloreactive T cell activation.

AUTHOR: Penna G; Adorini L
CORPORATE SOURCE: Roche Milano Ricerche, Milan, Italy.

SOURCE: JOURNAL OF IMMUNOLOGY, (2000 Mar 1) 164 (5) 2405-11.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Abridged Index Medicus Journals; Priority Journals
OTHER SOURCE: MEDLINE 2000143831
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000413
Last Updated on STN: 20000413

ABSTRACT:
1 Alpha,25-dihydroxyvitamin D3 (1,25(OH)2D3), the active form of vitamin D3, is a potent immunomodulatory agent. Here we show that dendritic cells (DCs) are major targets of 1,25(OH)2D3-induced immunosuppressive activity. 1,25(OH)2D3 prevents the differentiation in immature DCs of human monocytes cultured with GM-CSF and IL-4. Addition of 1,25(OH)2D3 during LPS-induced maturation maintains the immature DC phenotype characterized by high mannose receptor and low CD83 expression and markedly inhibits up-regulation of the costimulatory molecules CD40, CD80, and CD86 and of class II MHC molecules. This is associated with a reduced capacity of DCs to activate alloreactive T cells, as determined by decreased proliferation and IFN-gamma secretion in mixed leukocyte cultures. 1, 25(OH)2D3 also affects maturing DCs, leading to inhibition of IL-12p75 and enhanced IL-10 secretion upon activation by CD40 ligation. In addition, 1,25(OH)2D3 promotes the spontaneous apoptosis of mature DCs. The modulation of phenotype and function of DCs matured in the presence of 1,25(OH)2D3 induces cocultured alloreactive CD4+ cells to secrete less IFN-gamma upon restimulation, up-regulate CD152, and down-regulate CD154 molecules. The inhibition of DC differentiation and maturation as well as modulation of their activation and survival leading to T cell hyporesponsiveness may explain the immunosuppressive activity of 1, 25(OH)2D3.

CONTROLLED TERM: Check Tags: Human
Adjuvants, Immunologic: PD, pharmacology
Antigen Presentation: DE, drug effects
Antigens, Differentiation: BI, biosynthesis
Apoptosis: DE, drug effects
Apoptosis: IM, immunology
CD4-Positive T-Lymphocytes: DE, drug effects
CD4-Positive T-Lymphocytes: IM, immunology
CD4-Positive T-Lymphocytes: ME, metabolism
***Calcitriol: PD, pharmacology**
Cell Differentiation: DE, drug effects
Cell Differentiation: IM, immunology
Cell Line
Cell Survival: DE, drug effects
Cell Survival: IM, immunology
Cells, Cultured
Coculture
Dendritic Cells: CY, cytology
***Dendritic Cells: DE, drug effects**
*Dendritic Cells: IM, immunology
Dendritic Cells: ME, metabolism
*Growth Inhibitors: PD, pharmacology
Immune Tolerance: DE, drug effects
Interleukin-10: SE, secretion

Interleukin-12: AI, antagonists & inhibitors
Interleukin-12: SE, secretion
*Lymphocyte Transformation: DE, drug effects
*T-Lymphocytes: DE, drug effects
*T-Lymphocytes: IM, immunology
Up-Regulation: DE, drug effects
CAS REGISTRY NO.: 130068-27-8 (Interleukin-10); 187348-17-0 (Interleukin-12); 32222-06-3 (Calcitriol)
CHEMICAL NAME: 0 (Adjuvants, Immunologic); 0 (Antigens, Differentiation); 0 (CTLA-4); 0 (Growth Inhibitors)

L88 ANSWER 5 OF 49 CANCERLIT on STN DUPLICATE 19
ACCESSION NUMBER: 2000456969 CANCERLIT
DOCUMENT NUMBER: 20456969 PubMed ID: 11000289
TITLE: Bcl-2 transfected HaCaT keratinocytes resist apoptotic signals of ceramides, tumor necrosis factor alpha and 1 alpha, 25-dihydroxyvitamin D(3).
AUTHOR: Muller-Wieprecht V; Riebeling C; Stooss A; Orfanos C E; Geilen C C
CORPORATE SOURCE: Department of Dermatology, University Medical Center Benjamin Franklin, The Free University of Berlin, Fabeckstr. 60-62, 14195 Berlin, Germany.
SOURCE: ARCHIVES OF DERMATOLOGICAL RESEARCH, (2000 Sep) 292 (9) 455-62.
Journal code: 8000462. ISSN: 0340-3696.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
OTHER SOURCE: MEDLINE 2001039758
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010423
Last Updated on STN: 20010423

ABSTRACT:
During the last few years increasing evidence has shown that sphingolipid metabolites are highly bioactive compounds that play important roles in cellular regulation. The induction of ceramide signalling in primary human keratinocytes and HaCaT keratinocytes has recently been demonstrated using 1 alpha,25-dihydroxyvitamin D(3). The data obtained indicate that approximately one-third of the proapoptotic effect of 1 alpha,25-dihydroxyvitamin D(3) is mediated by an intracellular ceramide increase induced via tumor necrosis factor. expression and autocrine stimulation of sphingomyelin hydrolysis. In the present study the role of bcl-2 in this process was investigated. HaCaT keratinocytes were transfected with bcl-2 and the effects of C(2)-ceramide, tumor necrosis factor alpha and 1 alpha,25-dihydroxyvitamin D(3) on HaCaT keratinocytes stably overexpressing bcl-2 were determined. Apoptosis was measured by detection of soluble DNA-histone complexes using the ELISA technique. In situ analysis of apoptotic cells was also carried out by detecting phosphatidylserine flip using the annexin V method and by detecting DNA fragmentation using the TUNEL assay. The results obtained showed that apoptosis induced by C(2)-ceramide, tumor necrosis factor alpha or 1 alpha,25-dihydroxyvitamin D(3) occurred in a vector-transfected clone but not in a bcl-2-transfected HaCaT clone. This indicates the important role of bcl-2 in the regulation of ceramide-mediated signalling pathways in human keratinocytes and supports the involvement of ceramide as a signalling molecule in 1 alpha,25-dihydroxyvitamin D(3)-induced biological responses.

CONTROLLED TERM: Check Tags: Comparative Study; Human; Support, Non-U.S. Gov't
***Apoptosis**

Searched by Barb O'Bryen, STIC 2-2518

***Calcitriol: PD, pharmacology**
Cell Line
DNA Fragmentation
Dose-Response Relationship, Drug
Gene Expression Regulation: DE, drug effects
*Genes, bcl-2
Genetic Vectors
***Keratinocytes: DE, drug effects**
Keratinocytes: PH, physiology
Phosphatidylserines: AN, analysis
*Sphingosine: AA, analogs & derivatives
Sphingosine: PD, pharmacology
Transfection
*Tumor Necrosis Factor: PD, pharmacology
CAS REGISTRY NO.: 123-78-4 (Sphingosine); 32222-06-3 (Calcitriol)
CHEMICAL NAME: 0 (Genetic Vectors); 0 (N-acetylsphingosine); 0 (Phosphatidylserines); 0 (Tumor Necrosis Factor)

L88 ANSWER 6 OF 49 CANCERLIT on STN DUPLICATE 20
ACCESSION NUMBER: 2000387068 CANCERLIT
DOCUMENT NUMBER: 20387068 PubMed ID: 10926872
TITLE: 1 alpha,25-dihydroxyvitamin D(3) inhibits angiogenesis in vitro and in vivo.
AUTHOR: Mantell D J; Owens P E; Bundred N J; Mawer E B; Canfield A E
CORPORATE SOURCE: Wellcome Trust Centre for Cell Matrix Research, Department of Medicine University of Manchester, Manchester, UK.
SOURCE: CIRCULATION RESEARCH, (2000 Aug 4) 87 (3) 214-20. Journal code: 0047103. ISSN: 0009-7330.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
OTHER SOURCE: MEDLINE 2000419082
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20001012
Last Updated on STN: 20001012

ABSTRACT:
Modulation of angiogenesis is now a recognized strategy for the prevention and treatment of pathologies categorized by their reliance on a vascular supply. The purpose of this study was to evaluate the effect of 1 alpha,25-dihydroxyvitamin D(3) [1, 25(OH)(2)D(3)], the active metabolite of vitamin D(3), on angiogenesis by using well-characterized in vitro and in vivo model systems. 1,25(OH)(2)D(3) (1 x 10(-9) to 1 x 10(-7) mol/L) significantly inhibited vascular endothelial growth factor (VEGF)-induced endothelial cell sprouting and elongation in vitro in a dose-dependent manner and had a small, but significant, inhibitory effect on VEGF-induced endothelial cell proliferation. 1, 25(OH)(2)D(3) also inhibited the formation of networks of elongated endothelial cells within 3D collagen gels. The addition of 1, 25(OH)(2)D(3) to endothelial cell cultures containing sprouting elongated cells induced the regression of these cells, in the absence of any effect on cells present in the cobblestone monolayer. Analysis of nuclear morphology, DNA integrity, and enzymatic in situ labeling of apoptosis-induced strand breaks demonstrated that this regression was due to the induction of apoptosis specifically within the sprouting cell population. The effect of 1,25(OH)(2)D(3) on angiogenesis in vivo was investigated by using a model in which MCF-7 breast carcinoma cells, which had been induced to overexpress VEGF, were xenografted subcutaneously together with MDA-435S breast carcinoma cells into nude mice. Treatment with 1,25(OH)(2)D(3) (12.5 pmol/d for 8 weeks) produced tumors that were less well vascularized than tumors formed in mice

treated with vehicle alone. These results highlight the potential use of 1,25(OH)(2)D(3) in both the prevention and regression of conditions characterized by pathological angiogenesis.

CONTROLLED TERM: Check Tags: Animal; Female; Support, Non-U.S. Gov't
Adenocarcinoma: BS, blood supply
Adenocarcinoma: DT, drug therapy
Adenocarcinoma: PA, pathology
*Angiogenesis Inhibitors: PD, pharmacology
Angiogenesis Inhibitors: TU, therapeutic use
Antineoplastic Agents: PD, pharmacology
Antineoplastic Agents: TU, therapeutic use
Apoptosis: DE, drug effects
Breast Neoplasms: PA, pathology
***Calcitriol: PD, pharmacology**
Calcitriol: TU, therapeutic use
Cattle
Cell Division: DE, drug effects
Cells, Cultured: DE, drug effects
Endothelial Growth Factors: AI, antagonists & inhibitors
Endothelial Growth Factors: PD, pharmacology
Endothelium, Vascular: CY, cytology
Endothelium, Vascular: DE, drug effects
Lymphokines: AI, antagonists & inhibitors
Lymphokines: PD, pharmacology
Mice
Mice, Inbred BALB C
Mice, Nude
Morphogenesis: DE, drug effects
Neoplasm Transplantation
Neovascularization, Pathologic: DT, drug therapy
*Neovascularization, Physiologic: DE, drug effects
Transplantation, Heterologous
Tumor Cells, Cultured: TR, transplantation
CAS REGISTRY NO.: 32222-06-3 (Calcitriol)
CHEMICAL NAME: 0 (Angiogenesis Inhibitors); 0 (Antineoplastic Agents); 0 (Endothelial Growth Factors); 0 (Lymphokines); 0 (vascular permeability factor)

L88 ANSWER 7 OF 49 CANCERLIT on STN DUPLICATE 24
ACCESSION NUMBER: 1999126244 CANCERLIT
DOCUMENT NUMBER: 99126244 PubMed ID: 9929154
TITLE: Effects of trans-retinoic acid, 9-cis-retinoic acid, 1alpha,25-(dihydroxy)vitamin D3 and a novel apoptosis-inducing retinoid on breast cancer and endothelial cell growth.
AUTHOR: Dawson M I; Chao W R; Hobbs P D; Zhang X K
CORPORATE SOURCE: Retinoid Program, SRI International, Menlo Park, CA 94025, USA.. marciadawson@qm.sri.com
CONTRACT NUMBER: P01CA51993 (NCI)
SOURCE: CANCER LETTERS, (1998 Nov 13) 133 (1) 1-8.
Journal code: 7600053. ISSN: 0304-3835.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
OTHER SOURCE: MEDLINE 1999126244
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990405
Last Updated on STN: 19990405

ABSTRACT:
Breast cancer cell growth inhibition was not synergistically enhanced by trans-retinoic acid (RA) or 9-cis-RA plus 1alpha,25-(dihydroxy)vitamin D3 (DHVD). The retinoid/DHVD combinations did lower their 50% effective concentrations for inhibiting retinoid-sensitive MCF-7, but not retinoid-refractory BT-20, breast cancer cell growth. In contrast, the synthetic retinoid 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthalenecarboxylic acid (AHPN) and its analog SR11389 inhibited the growth of both cell lines. Unlike RA, 9-cis-RA and DHVD, AHPN and SR11389 also potently inhibited human umbilical vascular endothelial cell growth. These results on AHPN and SR11389 suggest that angiogenesis of tumor microvasculature should also be an effective therapeutic target for this new compound class.

CONTROLLED TERM: Check Tags: Female; Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
***Apoptosis: DE, drug effects**
*Breast Neoplasms: PA, pathology
***Calcitriol: PD, pharmacology**
Cell Division: DE, drug effects
Endothelium, Vascular: CY, cytology
***Endothelium, Vascular: DE, drug effects**
*Tretinoin: PD, pharmacology
Tumor Cells, Cultured
CAS REGISTRY NO.: 302-79-4 (Tretinoin); 32222-06-3 (Calcitriol); 5300-03-8 (9-cis-retinoic acid)

L88 ANSWER 8 OF 49 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2004613332 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15585637
TITLE: Inhibition of proliferation and induction of apoptosis by 25-hydroxyvitamin D3-3beta-(2)-Bromoacetate, a nontoxic and vitamin D receptor-alkylating analog of 25-hydroxyvitamin D3 in prostate cancer cells.
AUTHOR: Swamy Narasimha; Chen Tai C; Peleg Sara; Dhawan Puneet; Christakos Sylvia; Stewart Lamonica V; Weigel Nancy L; Mehta Rajendra G; Holick Michael F; Ray Rahul
CORPORATE SOURCE: Endocrinology, Diabetes and Nutrition, Department of Medicine, Boston University School of Medicine, 85 East Newton Street, Boston, MA 02118, USA.. bapi@bu.edu
CONTRACT NUMBER: DK 50583 (NIDDK)
SOURCE: Clinical cancer research : an official journal of the American Association for Cancer Research, (2004 Dec 1) 10 (23) 8018-27.
Journal code: 9502500. ISSN: 1078-0432.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200504
ENTRY DATE: Entered STN: 20041220
Last Updated on STN: 20050415
Entered Medline: 20050414

ABSTRACT:
The 25-hydroxyvitamin D(3) (25-OH-D(3)) is a nontoxic and low-affinity vitamin D receptor (VDR)-binding metabolic precursor of 1,25-dihydroxyvitamin D(3) [1,25(OH)(2)D(3)]. We hypothesized that covalent attachment of a 25-OH-D(3) analog to the hormone-binding pocket of VDR might convert the latter into transcriptionally active holo-form, making 25-OH-D(3) biologically active. Furthermore, it might be possible to translate the nontoxic nature of 25-OH-D(3) into its analog. We showed earlier that 25-hydroxyvitamin

D(3)-3-bromoacetate (25-OH-D(3)-3-BE) alkylated the hormone-binding pocket of VDR. In this communication we describe that 10(-6) mol/L of 25-OH-D(3)-3-BE inhibited the growth of keratinocytes, LNCaP, and LAPC-4 androgen-sensitive and PC-3 and DU145 androgen-refractory prostate cancer cells, and PZ-HPV-7 immortalized normal prostate cells with similar or stronger efficacy as 1,25(OH)(2)D(3). But its effect was strongest in LNCaP, PC-3, LAPC-4, and DU145 cells. Furthermore, 25-OH-D(3)-3-BE was toxic to these prostate cancer cells and caused these cells to undergo apoptosis as shown by DNA-fragmentation and caspase-activation assays. In a reporter assay with COS-7 cells, transfected with a 1alpha,25-dihydroxyvitamin D(3)-24-hydroxylase (24-OHase)-construct and VDR-expression vector, 25-OH-D(3)-3-BE induced 24-OHase promoter activity. In a "pull down assay" with PC-3 cells, 25-OH-D(3)-3-BE induced strong interaction between VDR and general transcription factors, retinoid X receptor, and GRIP-1. Collectively, these results strongly suggested that the cellular effects of 25-OH-D(3)-3-BE were manifested via 1,25(OH)(2)D(3)/VDR signaling pathway. A toxicity study in CD-1 mice showed that 166 microg/kg of 25-OH-D(3)-3-BE did not raise serum-calcium beyond vehicle control. Collectively, these results strongly suggested that 25-OH-D(3)-3-BE has a strong potential as a therapeutic agent for androgen-sensitive and androgen-refractory prostate cancer.

CONTROLLED TERM: Check Tags: Male
25-Hydroxyvitamin D3 1-alpha-Hydroxylase: GE, genetics
Animals
***Apoptosis: DE, drug effects**
COS Cells
*Calcitriol: AA, analogs & derivatives
***Calcitriol: PD, pharmacology**
Carrier Proteins: ME, metabolism
Caspases: ME, metabolism
*Cell Proliferation: DE, drug effects
Cercopithecus aethiops
Chloramphenicol O-Acetyltransferase
Dose-Response Relationship, Drug
Enzyme Activation: DE, drug effects
Humans
Keratinocytes: CY, cytology
Keratinocytes: DE, drug effects
Mice
*Neoplasms, Hormone-Dependent: DT, drug therapy
Neoplasms, Hormone-Dependent: PA, pathology
Nerve Tissue Proteins: ME, metabolism
Promoter Regions (Genetics)
Prostate: CY, cytology
Prostate: DE, drug effects
*Prostatic Neoplasms: DT, drug therapy
Prostatic Neoplasms: PA, pathology
Receptors, Calcitriol: ME, metabolism
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
Retinoid X Receptors: ME, metabolism
Thymidine: ME, metabolism
Tumor Cells, Cultured

CAS REGISTRY NO.: 32222-06-3 (Calcitriol); 50-89-5 (Thymidine)

CHEMICAL NAME: 0 (1,25-dihydroxyvitamin D3-3-bromoacetate); 0 (Carrier Proteins); 0 (GRIP1 protein, human); 0 (Nerve Tissue Proteins); 0 (Receptors, Calcitriol); 0 (Retinoid X Receptors); EC 1.14.- (25-Hydroxyvitamin D3 1-alpha-Hydroxylase); EC 2.3.1.28 (Chloramphenicol O-Acetyltransferase); EC 3.4.22.- (Caspases)

L88 ANSWER 9 OF 49 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2004324658 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15225814
TITLE: Anti-endothelial properties of 1,25-dihydroxy-3-epi-vitamin D3, a natural metabolite of calcitriol.
AUTHOR: Furigay Paul; Swamy Narasimha
CORPORATE SOURCE: Department of Pediatrics, Women and Infants' Hospital, Brown University, 101 Dudley Street, Providence, RI 02905, USA.
CONTRACT NUMBER: HD038774 (NICHD)
HD07511-04 (NICHD)
SOURCE: Journal of steroid biochemistry and molecular biology, (2004 May) 89-90 (1-5) 427-31.
Journal code: 9015483. ISSN: 0960-0760.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200408
ENTRY DATE: Entered STN: 20040701
Last Updated on STN: 20040901
Entered Medline: 20040831

ABSTRACT:
BACKGROUND: Calcitriol [1,25-(OH)(2)D(3)] is a strong anti-proliferative agent both in vitro and in vivo. Earlier studies have established that calcitriol inhibits the growth factor-stimulated proliferation of endothelial cells (EC) and angiogenesis. However, the lethal calcemic side effects of calcitriol prohibit its use as a therapeutic agent. Several analogs of vitamin D have been developed to minimize these calcemic side effects. 1,25-dihydroxy-3-epi-vitamin D(3) (3-epiD(3)), a naturally formed vitamin D metabolite is one such analog. OBJECTIVE: To demonstrate that 3-epiD(3), a calcitriol analog, inhibits endothelial cell proliferation and induces apoptosis. RESULTS: Treatment of EC with 3-epiD(3) showed 60% inhibition ($P < 0.006$) of proliferation. Cell viability assays corroborated these results. Pro-apoptotic caspase-3 activity was increased fourfold ($P < 0.01$) in 3-epiD(3)-treated cells over controls. 3-epiD(3) induced apoptosis in EC as shown by genomic DNA fragmentation. Cell cycle analysis of 3-epiD(3)-treated EC revealed a G0/G1 arrest. CONCLUSIONS: 3-epiD(3), a low-calcemic, natural analog of calcitriol, inhibits EC proliferation by causing a G0/G1 arrest and induces apoptosis more effectively than 1,25-(OH)(2)D(3). These results suggest that 3-epiD(3) is a potent inhibitor of EC growth.

CONTROLLED TERM: **Apoptosis: DE, drug effects**
Caspases: ME, metabolism
Cell Division: DE, drug effects
Cells, Cultured
*Cholecalciferol: AA, analogs & derivatives
***Cholecalciferol: PD, pharmacology**
Endothelium, Vascular: CY, cytology
***Endothelium, Vascular: DE, drug effects**
Enzyme Activation
Humans
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
CAS REGISTRY NO.: 1173-13-3 (previtamin D(3)); 67-97-0 (Cholecalciferol)
CHEMICAL NAME: EC 3.4.22.- (Caspases); EC 3.4.22.- (caspase-3)

L88 ANSWER 10 OF 49 MEDLINE on STN DUPLICATE 9
ACCESSION NUMBER: 2003342061 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12874825
TITLE: 1alpha,25-Dihydroxyvitamin D3-3beta-(2)-bromoacetate, an

affinity labeling derivative of 1alpha,25-dihydroxyvitamin D3 displays strong antiproliferative and cytotoxic behavior in prostate cancer cells.

AUTHOR: Swamy Narasimha; Persons Kelly S; Chen Tai C; Ray Rahul
CORPORATE SOURCE: Section in Endocrinology, Diabetes and Metabolism, Department of Medicine, Boston University School of Medicine, 85 East Newton Street, Boston, MA 02118, USA.

SOURCE: Journal of cellular biochemistry, (2003 Aug 1) 89 (5) 909-16.
Journal code: 8205768. ISSN: 0730-2312.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200311
ENTRY DATE: Entered STN: 20030723
Last Updated on STN: 20031218
Entered Medline: 20031118

ABSTRACT:
In this report we describe that 1,25(OH)(2)D(3)-3-BE, a VDR-affinity labeling analog of 1,25(OH)(2)D(3), showed strong and dose-dependent growth-inhibitory effect in several epithelial cells, i.e., keratinocytes (primary cells), MCF-7 breast cancer, PC-3, and LNCaP prostate cancer and PZ-HPV-7 immortalized normal prostate cell-lines. Furthermore, 10(-6) M of 1,25(OH)(2)D(3)-3-BE induced apoptosis specifically in LNCaP and PC-3 cells; and the effect was much less pronounced at lower doses. We also showed that the effect (of 1,25(OH)(2)D(3)-3-BE) was not due to probable degradation (hydrolysis) of 1,25(OH)(2)D(3)-3-BE or random interaction of this molecule with cellular proteins. Tissue- or cell-specific action of 1,25(OH)(2)D(3) and its mimics is not common due to the ubiquitous nature of VDR. Furthermore, variable effects of 1,25(OH)(2)D(3) and its analogs in various cell-lines potentially limits their application as anticancer agents. We showed that 1,25(OH)(2)D(3)-3-BE displayed similar growth-inhibitory and cytotoxic activities towards androgen sensitive LNCaP and androgen-independent PC-3 cell-lines. Therefore, these results raise the possibility that 1,25(OH)(2)D(3)-3-BE or similar VDR-cross linking analogs of 1,25(OH)(2)D(3) might be considered for further development as potential candidates for prostate cancer.

CONTROLLED TERM: Check Tags: Female; Male
Affinity Labels: CH, chemistry
Affinity Labels: PD, pharmacology
Apoptosis: DE, drug effects
Breast Neoplasms: DT, drug therapy
Breast Neoplasms: PA, pathology
*Calcitriol: AA, analogs & derivatives
Calcitriol: ME, metabolism
***Calcitriol: PD, pharmacology**
Cell Division: DE, drug effects
Cell Line
Cell Survival: DE, drug effects
Dose-Response Relationship, Drug
Epithelial Cells: DE, drug effects
Epithelial Cells: ME, metabolism
Flow Cytometry
Humans
Keratinocytes: CY, cytology
Keratinocytes: DE, drug effects
Methylene Blue: CH, chemistry
Prostate: CY, cytology
Prostate: DE, drug effects

*Prostatic Neoplasms: DT, drug therapy
Prostatic Neoplasms: PA, pathology
Receptors, Calcitriol: CH, chemistry
Receptors, Calcitriol: ME, metabolism
Research Support, Non-U.S. Gov't
Thymidine: ME, metabolism

CAS REGISTRY NO.: 32222-06-3 (Calcitriol); 50-89-5 (Thymidine); 61-73-4 (Methylene Blue)

CHEMICAL NAME: 0 (1,25-dihydroxyvitamin D3-3-bromoacetate); 0 (Affinity Labels); 0 (Receptors, Calcitriol)

L88 ANSWER 11 OF 49 MEDLINE on STN DUPLICATE 10

ACCESSION NUMBER: 2003538088 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14617105
TITLE: Enhancement of photodynamic effect in normal rat keratinocytes by treatment with 1,25 dihydroxy vitamin D3.
AUTHOR: Matsuyama Asako; Nakano Hajime; Harada Ken; Yamazaki Takehiko; Kanno Takahiro; Wakui Makoto; Hanada Katsumi
CORPORATE SOURCE: Department of Dermatology, Hirosaki University School of Medicine, Hirosaki, Japan.
SOURCE: Photodermatology, photoimmunology & photomedicine, (2003 Dec) 19 (6) 303-8.
Journal code: 9013641. ISSN: 0905-4383.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200403
ENTRY DATE: Entered STN: 20031118
Last Updated on STN: 20040330
Entered Medline: 20040329

ABSTRACT:
BACKGROUND: To better understand the pathogenesis of photodynamic therapy (PDT)-induced apoptosis cytosolic calcium [Ca2+]i was measured using cultured fetal rat keratinocytes (FRSKs). Moreover, the influence of 1,25 dihydroxy vitamin D3 (1,25(OH)2D3) with the action of increasing [Ca2+]i on the PDT effect was studied. METHODS: FRSKs were treated with a medium containing the photosensitizer, aluminum phthalocyanine tetrasulfonate (AlPcTs), and were then exposed to selective visible light derived from a halogen lamp. Electrophoresis of DNA extracted from the PDT-treated cells revealed DNA fragmentation, a sign of apoptosis in cultured FRSKs under the condition with or without 1,25(OH)2D3. RESULTS: PDT-treated FRSKs exhibited increased levels of [Ca2+]i; these levels were significantly elevated further by the treatment of cells with 1,25(OH)2D3. However, cells treated with ethylene glycol bis (b-aminoethyl ether)-N,N,N',N'-tetraacetic acid (EGTA), a chelator of extracellular calcium, prior to PDT did not show any DNA fragmentation either in the presence or absence of 1,25(OH)2D3. CONCLUSION: PDT-induced apoptosis in FRSKs may be caused by the influx of extracellular calcium. Addition of 1,25(OH)2D3 clearly enhanced the DNA fragmentation in the cultured FRSKs, indicating the effect of increased [Ca2+]i. The combination therapy of AlPcTs-PDT with the administration of 1,25(OH)2D3 may contribute to the enhancement of the AlPcTs-PTD effect.

CONTROLLED TERM: Animals
Apoptosis: DE, drug effects
Apoptosis: RE, radiation effects
Calcitriol: AD, administration & dosage
***Calcitriol: PD, pharmacology**
Calcium: AD, administration & dosage
*Calcium: PD, pharmacology
DNA: AN, analysis

Searched by Barb O'Bryen, STIC 2-2518

DNA Fragmentation: DE, drug effects
DNA Fragmentation: RE, radiation effects
Embryo
***Keratinocytes: DE, drug effects**
Keratinocytes: ME, metabolism
*Keratinocytes: RE, radiation effects
Photochemotherapy
Rats
*Ultraviolet Rays
CAS REGISTRY NO.: 32222-06-3 (Calcitriol); 7440-70-2 (Calcium); 9007-49-2 (DNA)

L88 ANSWER 12 OF 49 MEDLINE on STN DUPLICATE 18
ACCESSION NUMBER: 2001139087 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11194893
TITLE: Comparative inhibitory effects of vitamin D3 and an analogue on normal and psoriatic epidermis in organ culture.
AUTHOR: Kondo S; Hozumi Y; Mitsuhashi Y
CORPORATE SOURCE: Department of Dermatology, Yamagata University School of Medicine, Iida-Nishi, Yamagata City, Japan.. skondo@med.id.yamagata-u.ac.jp
SOURCE: Archives of dermatological research, (2000 Nov) 292 (11) 550-5.
Journal code: 8000462. ISSN: 0340-3696.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20030313
Entered Medline: 20010308

ABSTRACT:
Recently, there have been many vitamin D3 analogues synthesized and tried in the treatment of psoriasis. In the experiments reported here we observed and compared their effects on normal and psoriatic epidermis in organ culture in vitro. We employed a new vitamin D3 analogue, 22-oxa-calcitriol (OCT), the effect of which was compared with that of calcitriol (1,25-D3). Both caused suppression of proliferation of normal and psoriatic epidermis, dependent upon concentration and culture time. Histologically, in the presence of the agents, degeneration started from the top of the epidermis downwards. This is the first report of cell degeneration as a direct effect of vitamin D. The nature of the degeneration was evaluated by electron microscopy (EM) and by the in situ nick end labeling technique (TUNEL), and these studies revealed that the degeneration involved necrosis rather than apoptosis. This in vitro method may be useful to assess the effectiveness of newly synthesized vitamin D3 analogues in the treatment of psoriasis.

CONTROLLED TERM: Check Tags: Comparative Study
Apoptosis: DE, drug effects
Bromodeoxyuridine: ME, metabolism
*Calcitriol: AA, analogs & derivatives
Calcitriol: PD, pharmacology
Cholecalciferol: AA, analogs & derivatives
***Cholecalciferol: PD, pharmacology**
Dermatologic Agents: PD, pharmacology
Dose-Response Relationship, Drug
***Epidermis: DE, drug effects**
Epidermis: GD, growth & development
Epidermis: UL, ultrastructure

Humans
Microscopy, Electron
Organ Culture Techniques
Psoriasis: ME, metabolism
Psoriasis: PA, pathology
*Psoriasis: PC, prevention & control
CAS REGISTRY NO.: 103909-75-7 (maxacalcitol); 32222-06-3 (Calcitriol); 59-14-3 (Bromodeoxyuridine); 67-97-0 (Cholecalciferol); 87480-00-0 (1,25-dihydroxy-23-thiavitamin D3)
CHEMICAL NAME: 0 (Dermatologic Agents)

L88 ANSWER 13 OF 49 MEDLINE on STN
ACCESSION NUMBER: 2004425366 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15331408
TITLE: Vitamin D3 induces caspase-14 expression in psoriatic lesions and enhances caspase-14 processing in organotypic skin cultures.
AUTHOR: Lippens Saskia; Kockx Mark; Denecker Geertrui; Knaapen Michiel; Verheyen An; Christiaen Ruben; Tschachler Erwin; Vandenabeele Peter; Declercq Wim
CORPORATE SOURCE: Department of Molecular Biomedical Research, Molecular Signaling and Cell Death Unit, Flanders Interuniversity Institute for Biotechnology (VIB) and Ghent University, Zwijnaarde, Belgium.
SOURCE: American journal of pathology, (2004 Sep) 165 (3) 833-41. Journal code: 0370502. ISSN: 0002-9440.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200409
ENTRY DATE: Entered STN: 20040828
Last Updated on STN: 20041001
Entered Medline: 20040930

ABSTRACT:
Caspase-14 is a nonapoptotic caspase family member whose expression in the epidermis is confined to the suprabasal layers, which consist of differentiating keratinocytes. Proteolytic activation of this caspase is observed in the later stages of epidermal differentiation. In psoriatic skin, a dramatic decrease in caspase-14 expression in the parakeratotic plugs was observed. Topical treatment of psoriatic lesions with a vitamin D3 analogue resulted in a decrease of the psoriatic phenotype and an increase in caspase-14 expression in the parakeratotic plugs. To investigate whether vitamin D3 directly affects caspase-14 expression levels, we used keratinocyte cell cultures. 1alpha,25-Dihydroxycholecalciferol, the biologically active form of vitamin D3, increased caspase-14 expression, whereas retinoic acid inhibited it. Moreover, retinoic acid repressed the vitamin D3-induced caspase-14 expression level. In addition, the use of organotypic skin cultures demonstrated that 1alpha,25-dihydroxycholecalciferol enhanced epidermal differentiation and caspase-14 activation, whereas retinoic acid completely blocked caspase-14 processing. Our data indicate that caspase-14 plays an important role in terminal epidermal differentiation, and its absence may contribute to the psoriatic phenotype.
CONTROLLED TERM: Check Tags: Comparative Study; Female; Male
Adolescent
Adult
Aged
Apoptosis: DE, drug effects
Caspases: AI, antagonists & inhibitors
*Caspases: ME, metabolism

Cell Differentiation: DE, drug effects
***Cholecalciferol: PD, pharmacology**
Enzyme Activation: DE, drug effects
Epidermis: DE, drug effects
*Epidermis: EN, enzymology
Humans
Keratinocytes: DE, drug effects
*Keratinocytes: EN, enzymology
Middle Aged
Organ Culture Techniques
Phenotype
*Psoriasis: EN, enzymology
Psoriasis: PA, pathology
Research Support, Non-U.S. Gov't
Thymidine: ME, metabolism
Tretinoin: PD, pharmacology

CAS REGISTRY NO.: 302-79-4 (Tretinoin); 50-89-5 (Thymidine); 67-97-0 (Cholecalciferol)
CHEMICAL NAME: EC 3.4.22.- (Caspases); EC 3.4.22.- (caspase 14)

L88 ANSWER 14 OF 49 MEDLINE on STN
ACCESSION NUMBER: 2003344930 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12858333
TITLE: 1,25-Dihydroxyvitamin D3 inhibits ultraviolet B-induced apoptosis, Jun kinase activation, and interleukin-6 production in primary human keratinocytes.
AUTHOR: De Haes Petra; Garmyn Marjan; Degreef Hugo; Vantieghem Katleen; Bouillon Roger; Segaert Siegfried
CORPORATE SOURCE: Laboratory for Experimental Medicine and Endocrinology (LEGENDO), Gasthuisberg, Katholieke Universiteit Leuven, 3000 Leuven, Belgium.
SOURCE: Journal of cellular biochemistry, (2003 Jul 1) 89 (4) 663-73.
Journal code: 8205768. ISSN: 0730-2312.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200311
ENTRY DATE: Entered STN: 20030725
Last Updated on STN: 20031218
Entered Medline: 20031117

ABSTRACT:
We investigated the capacity of 1,25-dihydroxyvitamin D(3) [1,25(OH)(2)D(3)] to protect human keratinocytes against the hazardous effects of ultraviolet B (UVB)-irradiation, recognized as the most important etiological factor in the development of skin cancer. Cytoprotective effects of 1,25(OH)(2)D(3) on UVB-irradiated keratinocytes were seen morphologically and quantified using a colorimetric survival assay. Moreover, 1,25(OH)(2)D(3) suppressed UVB-induced apoptotic cell death. An ELISA, detecting DNA-fragmentation, demonstrated that pretreatment of keratinocytes with 1,25(OH)(2)D(3) 1 microM for 24 h reduced UVB-stimulated apoptosis by 55-70%. This suppression required pharmacological concentrations 1,25(OH)(2)D(3) and a preincubation period of several hours. In addition, 1,25(OH)(2)D(3) also inhibited mitochondrial cytochrome c release (90%), a hallmark event of UVB-induced apoptosis. Furthermore, we demonstrated that 1,25(OH)(2)D(3) reduced two important mediators of the UV-response, namely, c-Jun-NH(2)-terminal kinase (JNK) activation and interleukin-6 (IL-6) production. As shown by Western blotting, pretreatment of keratinocytes with 1,25(OH)(2)D(3) 1 microM diminished UVB-stimulated JNK activation with more than 30%. 1,25(OH)(2)D(3) treatment (1 microM) reduced UVB-induced IL-6 mRNA

expression and secretion with 75-90%. Taken together, these findings suggest the existence of a photoprotective effect of active vitamin D(3) and create new perspectives for the pharmacological use of active vitamin D compounds in the prevention of UVB-induced skin damage and carcinogenesis.

CONTROLLED TERM:
***Apoptosis: DE, drug effects**
Apoptosis: RE, radiation effects
Blotting, Northern
Blotting, Western
***Calcitriol: PD, pharmacology**
Cell Survival: DE, drug effects
Cell Survival: RE, radiation effects
Cytochromes c: BI, biosynthesis
Cytochromes c: RE, radiation effects
Dose-Response Relationship, Drug
Enzyme Activation: DE, drug effects
Enzyme Activation: RE, radiation effects
Enzyme-Linked Immunosorbent Assay
Humans
*Interleukin-6: BI, biosynthesis
Interleukin-6: RE, radiation effects
JNK Mitogen-Activated Protein Kinases
Keratinocytes: CY, cytology
***Keratinocytes: DE, drug effects**
Keratinocytes: ME, metabolism
*Keratinocytes: RE, radiation effects
Microscopy, Fluorescence
*Mitogen-Activated Protein Kinases: ME, metabolism
Mitogen-Activated Protein Kinases: RE, radiation effects
Research Support, Non-U.S. Gov't
Tumor Necrosis Factor-alpha: BI, biosynthesis
Tumor Necrosis Factor-alpha: RE, radiation effects
Ultraviolet Rays
Up-Regulation: RE, radiation effects

CAS REGISTRY NO.: 32222-06-3 (Calcitriol); 9007-43-6 (Cytochromes c)
CHEMICAL NAME: 0 (Interleukin-6); 0 (Tumor Necrosis Factor-alpha); EC 2.7.1.37 (JNK Mitogen-Activated Protein Kinases); EC 2.7.1.37 (Mitogen-Activated Protein Kinases)

L88 ANSWER 15 OF 49 MEDLINE on STN
ACCESSION NUMBER: 2003365230 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12899540
TITLE: Modulation of X-ray-induced apoptosis in human keratinocytes (HaCaT) by 1,25-dihydroxyvitamin D3.
AUTHOR: Meineke Viktor; Pfaffendorf Carolina; Schinn Michaela; Tilgen Wolfgang; Mayerhofer Artur; Dimitrijevic Nicola; van Beuningen Dirk; Reichrath Jorg
CORPORATE SOURCE: Institut fur Radiobiologie der Bundeswehr, 80937 Munich, Germany.. Viktor.Meineke@t-online.de
SOURCE: Recent results in cancer research. Fortschritte der Krebsforschung. Progres dans les recherches sur le cancer, (2003) 164 427-32.
Journal code: 0044671. ISSN: 0080-0015.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200312
ENTRY DATE: Entered STN: 20030806
Last Updated on STN: 20031218

Entered Medline: 20031204

ABSTRACT:
Possible effects of 1,25-dihydoxyvitamin D3 (vitamin D) on ionizing radiation-induced cell damage have been unknown until now. The task of the present study was to analyze, in a human keratinocyte cell line (HaCaT), the effects of a preincubation with vitamin D on the X-ray-induced mRNA expression of different genes related to apoptosis (gene array). The first results show that ionizing radiation leads to a down-regulation of various apoptosis-relevant genes in HaCaT cells pretreated with vitamin D. Therefore it can be speculated that vitamin D could prove to be a promising radioprotective substance.

CONTROLLED TERM: ***Apoptosis: RE, radiation effects**
***Calcitriol: PD, pharmacology**
Cells, Cultured: DE, drug effects
Cells, Cultured: RE, radiation effects
Down-Regulation
Gene Expression Profiling
Humans
***Keratinocytes: DE, drug effects**
Keratinocytes: ME, metabolism
Keratinocytes: PA, pathology
Oligonucleotide Array Sequence Analysis
RNA, Messenger: ME, metabolism
*Radiation-Protective Agents: PD, pharmacology
X-Rays

CAS REGISTRY NO.: 32222-06-3 (Calcitriol)
CHEMICAL NAME: 0 (RNA, Messenger); 0 (Radiation-Protective Agents)

L88 ANSWER 16 OF 49 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN DUPLICATE 1

ACCESSION NUMBER: 2005-11852 DRUGU P V
TITLE: Growth suppression of **ovarian** cancer xenografts in nude mice by vitamin D analogue EB1089.
AUTHOR: Zhang X; Jiang F; Li P; Li C; Ma Q; Nicosia S V; Bai W
CORPORATE SOURCE: Univ.South-Florida
LOCATION: Tampa, FL, USA
SOURCE: Clin.Cancer Res. (11, No. 1, 323-28, 2005) 4 Fig. 21 Ref.
CODEN: CCREF ISSN: 1078-0432
AVAIL. OF DOC.: Department of Pathology, University of South Florida College of Medicine, 12901 Bruce B. Downs Boulevard, MDC 11, Tampa, FL 33612-4799, U.S.A. (W.B.). (e-mail: wbai@hsc.usf.edu).
LANGUAGE: English
DOCUMENT TYPE: Journal

ABSTRACT:

EB-1089 (seocalcitol, Leo), at concentrations lower than 1,25-dihydroxyvitamin D3 (1,25(OH)2D3, Calbiochem), suppressed the growth of **ovarian** cancer OVCAR-3 and BG-1 cells and transcriptionally activated the GADD45 reporter gene in-vitro. EB-1089 also induced apoptosis in these **ovarian** cancer cells. P.o. EB-1089 inhibited tumor growth without causing hypercalcemia in nude mice bearing OVCAR-3 tumor xenografts in-vivo. EB-1089 altered tumor histology, reduced proliferation index, and increased apoptosis of ***ovarian*** tumor cells. Data suggest continued development of 1,25(OH)2D3 analogs for possible use as an alternative or complementary therapy for human ***ovarian*** cancer.

SECTION HEADING: P Pharmacology
V Vitamins

CLASSIF. CODE: **42 Vitamins**
52 Chemotherapy - non-clinical

CONTROLLED TERM:
[01] SEOCALCITOL *PH; LEO *FT; OVCAR3 *OC; ANIMAL-NEOPLASM *OC; **OVARY**-DISEASE *OC; **OVARY** *OC; CALCITRIOL *RC; **EB-1089** *RN; IN-VITRO *FT; OVCAR3-CELL *FT; BG1-CELL *FT; GADD45 *FT; **APOPTOSIS** *FT; **APOPTOSIS-INDUCER** *FT; CYTOSTATIC *FT; P.O. *FT; IN-VIVO *FT; XENOGRAFT *FT; MOUSE *FT; HISTOLOGY *FT; TUMOR-CELL *FT; TISSUE-CULTURE *FT; CARCINOMA *FT; LAB.ANIMAL *FT; **VITAMINS-D** *FT; CYTOSTATICS *FT; PH *FT
CAS REGISTRY NO.: 134404-52-7
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

L88 ANSWER 17 OF 49 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-31580 DRUGU P V
TITLE: The combination of a potent vitamin D3 analog, EB 1089, with ionising radiation reduces tumor growth and induces apoptosis of MCF-7 breast tumor xenografts in nude mice.
AUTHOR: Sundaram S; Sea A; Feldman S; Strawbridge R; Hoopes P J; Demidenko E; Binderup L; Gewirtz D A
CORPORATE SOURCE: Dartmouth-Coll.; Leo; Univ.Virginia-Commonwealth
LOCATION: Lebanon, N.H.; Richmond, Va., USA; Ballerup, Den.
SOURCE: Clin.Cancer Res. (9, No. 6, 2350-56, 2003) 4 Fig. 37 Ref.
CODEN: CCREF ISSN: 1078-0432
AVAIL. OF DOC.: Department of Surgery, Dartmouth Medical School, One Medical Center Drive, HB 7850, Lebanon, NH 03756, U.S.A. (e-mail: Sujatha.Sundaram@dartmouth.edu).
LANGUAGE: English
DOCUMENT TYPE: Journal

ABSTRACT:

A combination of continuous i.v. EB-1089 (seocalcitol) for 8 days followed by ionizing radiation for 3 days was associated with suppression of human breast MCF-7 tumor growth and proliferation, a higher rate of decline in tumor volume, loss of cellularity, and apoptosis in **ovariectomized** nude mice bearing MCF-7 tumors and implanted s.c. with 17-beta-estradiol. Data suggest EB-1089 can improve local tumor control by fractionated radiation, in part through the promotion of apoptotic cell death.

SECTION HEADING: P Pharmacology
V Vitamins

CLASSIF. CODE: **42 Vitamins**
52 Chemotherapy - non-clinical

CONTROLLED TERM:
[01] SEOCALCITOL *PH; MCF7 *OC; NEOPLASM *OC; ESTRADIOL *RC; **EB-1089** *RN; IN-VIVO *FT; MOUSE *FT; CONTINUOUS *FT; I.V. *FT; INFUSION *FT; CYTOSTATIC *FT; **APOPTOSIS-INDUCER** *FT; COMB. *FT; IRRADIATION *FT; LAB.ANIMAL *FT; INJECTION *FT; **VITAMINS-D** *FT; CYTOSTATICS *FT; PH *FT
CAS REGISTRY NO.: 134404-52-7
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

L88 ANSWER 18 OF 49 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-29374 DRUGU P
TITLE: Selective enhancement of radiation responsiveness and apoptosis in MCF-7 breast tumor cells by the vitamin D3 analog, EB 1089.
AUTHOR: Gupta M S; Wang H; Cabot M; Gennings C; park M; Gewirtz D A
CORPORATE SOURCE: Univ.Virginia-Commonwealth; John-Wayne-Cancer-Inst.
LOCATION: Richmond, Va.; Santa Monica, Cal., USA
SOURCE: Proc.Am.Assoc.Cancer Res. (43, 93 Meet., 649, 2002) ISSN: 0197-016X
AVAIL. OF DOC.: Virginia Commonwealth University Medical College Virginia, Richmond, VA, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal

ABSTRACT:

The effects of EB-1089 with fractionated ionizing radiation were studied in MCF7 cells. EB-1089 alone at 100 nM or followed by 5 x 2 Gy fractionated radiated were given to MCF7 cells. The results showed that the combination of EB-1089 with fractionated radiation prompted apoptosis and induced senescence in the breast tumor cell both of which could be linked to the generation of ceramide. (conference abstract: 93rd Annual Meeting of the American Association for Cancer Research, San Francisco, California, USA, 2002).

SECTION HEADING: P Pharmacology

CLASSIF. CODE: 52 Chemotherapy - non-clinical
73 Trial Preparations

CONTROLLED TERM:
[01] SEOCALCITOL *PH; **EB-1089** *RN; MCF7-CELL *FT; IN-VITRO *FT; TUMOR-CELL *FT; **APOPTOSIS** *FT; IRRADIATION *FT; **APOPTOSIS** *FT; **APOPTOSIS-INDUCER** *FT; FIBROBLAST *FT; **EPITHELIUM** *FT; TISSUE-CULTURE *FT; TUMOR-CELL *FT; CARCINOMA *FT; TISSUE-CULTURE *FT; **VITAMINS-D** *FT; CYTOSTATICS *FT; PH *FT
CAS REGISTRY NO.: 134404-52-7
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

L88 ANSWER 19 OF 49 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2004:739959 CAPLUS
DOCUMENT NUMBER: 141:237098
TITLE: **Prevention** of **ovarian** cancer by administration of products that induce biologic effects in the **ovarian** epithelium
INVENTOR(S): Rodriguez, Gustavo C.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 43 pp., Cont.-in-part of U. S. Ser. No. 798,453.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 8
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004176336	A1	20040909	US 2004-802273	20040317
US 2003125229	A1	20030703	US 2000-528963	20000321
US 6765002	B2	20040720		
US 6511970	B1	20030128	US 2000-672735	20000928
US 2001044431	A1	20011122	US 2001-798453	20010302
PRIORITY APPLN. INFO.:			US 2000-528963	A2 20000321
			US 2000-532340	B2 20000321
			US 2000-672735	A2 20000928
			US 2001-798453	A2 20010302
			US 1996-713834	A1 19960913
			US 1997-873010	A1 19970611
			US 1998-118143	A2 19980716
			US 1999-464899	A2 19991216
			US 2000-479021	A2 20000107

ED Entered STN: 10 Sep 2004

AB The invention relates to compns. and methods for preventing the development of epithelial ovarian cancer. Enhanced HRT and OCP regimens and formulations are also disclosed.

IT **1406-16-2**, Vitamin D **32511-63-0**, 1,25-Dihydroxyvitamin D3
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(prevention of **ovarian** cancer by administration of products that induce biol. effects in **ovarian** epithelium)

L88 ANSWER 20 OF 49 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 11

ACCESSION NUMBER: 2003:164493 CAPLUS
DOCUMENT NUMBER: 139:47511
TITLE: Chemoprevention of mammary carcinogenesis by 1α-hydroxyvitamin D5, a synthetic analog of Vitamin D
AUTHOR(S): Mehta, Rajendra G.; Hussain, Erum A.; Mehta, Rajeshwari R.; Das Gupta, Tapas K.
CORPORATE SOURCE: College of Medicine, Department of Surgical Oncology, University of Illinois at Chicago, Chicago, IL, 60612, USA
SOURCE: Mutation Research (2003), 523-524, 253-264
CODEN: MUREAV; ISSN: 0027-5107
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

ED Entered STN: 05 Mar 2003

AB Numerous analogs of Vitamin D have been synthesized in recent years with the hope of generating a compound that retains the anticarcinogenic activity of Vitamin D without causing any toxicity. The authors synthesized such an analog, 1α-hydroxy-24-ethylcholecalciferol [1α-hydroxyvitamin D5 or 1α(OH)D5], and showed that it was tolerated by rats and mice at a much higher dose than 1α,25 dihydroxy cholecalciferol [1α,25(OH)2D3]. This property makes it a prime candidate for chemoprevention studies. In the mouse mammary gland organ culture (MMOC), 1α(OH)D5 inhibited carcinogen-induced development of both mammary alveolar and ductal lesions. In vivo carcinogenesis study showed statistically significant reduction of tumor incidence and multiplicity in N-methyl-N-nitrosourea (MNU)-treated rats that were fed 25-50 μg 1α(OH)D5/kg diet. There were no adverse effects on plasma calcium concns. To determine if the effect of 1α(OH)D5 would be selective in suppressing proliferation of transformed cells, its effects on cell growth

and proliferation were compared between BT474 (cancer) and MCF12F (non-tumorigenic) human breast epithelial cells. Results showed that 1α(OH)D5 induced apoptosis and cell cycle G1 phase arrest in BT474 breast cancer cells without having any effects on proliferation of the MCF12F cells. In addition, in MMOC it had no growth inhibitory effects on normal epithelial cell proliferation in the absence of carcinogen. Similarly, non-tumorigenic human breast epithelial cells in explant culture did not respond to 1α(OH)D5, whereas treatment with 1α(OH)D5 induced cell death in the explants of cancer tissue. These results collectively indicate that 1α(OH)D5 selectively induced apoptosis only in transformed cells but not in normal breast epithelial cells. Interestingly, the growth inhibitory effects of 1α(OH)D5 were observed in Vitamin D receptor pos. (VDR+) breast cancer cells, but not in highly metastatic VDR- breast cancer cells, such as MDA-MB-435 and MDA-MB-231, suggesting that 1α(OH)D5 action may be mediated, in part, by VDR.

IT **1406-16-2**, Vitamin D **32222-06-3**, 1α,25 Dihydroxy cholecalciferol
RL: BSU (Biological study, unclassified); **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(chemoprevention of mammary carcinogenesis by synthetic analog of Vitamin D 1α-hydroxyvitamin D5)

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L88 ANSWER 21 OF 49 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 16
ACCESSION NUMBER: 2000:157711 CAPLUS
DOCUMENT NUMBER: 132:161246
TITLE: **Prevention** of **ovarian** cancer by administration of a vitamin D compound
INVENTOR(S): Rodriguez, Gustavo C.; Whitaker, Regina Salas
PATENT ASSIGNEE(S): New Life Pharmaceuticals Inc., USA
SOURCE: U.S., 9 pp., Cont.-in-part of U.S. Ser. No. 713,834.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 8
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6034074	A	20000307	US 1997-873010	19970611
US 6028064	A	20000222	US 1996-713834	19960913
CA 2293582	AA	19981217	CA 1998-2293582	19980605
WO 9856389	A1	19981217	WO 1998-US11737	19980605
W: AU, BR, CA, CN, JP, MX, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9878222	A1	19981230	AU 1998-78222	19980605
EP 983070	A1	20000308	EP 1998-926371	19980605
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6407082	B1	20020618	US 2000-479837	20000107
US 6444658	B1	20020903	US 2000-479021	20000107
US 6511970	B1	20030128	US 2000-672735	20000928
US 2002061867	A1	20020523	US 2002-51662	20020118
US 2004167106	A1	20040826	US 2004-781173	20040218
PRIORITY APPLN. INFO.:			US 1996-713834	A2 19960913
			US 1997-873010	A 19970611

WO 1998-US11737	W	19980605
US 1998-118143	A2	19980716
US 1999-464899	A2	19991216
US 2000-479021	A2	20000107
US 2000-479837	A1	20000107
US 2000-528963	A2	20000321
US 2000-532340	B2	20000321
US 2002-51662	A1	20020118

ED Entered STN: 09 Mar 2000

AB Methods are provided for preventing the development of epithelial ovarian cancer by administering a Vitamin D compound, e.g. 1,25-dihydroxyvitamin D3, in an amount capable of increasing apoptosis in nonneoplastic ovarian epithelial cells of the female subject.

IT **1406-16-2D**, Vitamin D, derivs. **32222-06-3**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(vitamin D compound for prevention of **ovarian** cancer)

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L88 ANSWER 22 OF 49 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 22
ACCESSION NUMBER: 1999:7831 CAPLUS
DOCUMENT NUMBER: 130:47470
TITLE: **Prevention** of **ovarian** cancer by administration of a vitamin D compound
INVENTOR(S): Rodriguez, Gustavo C.; Whitaker, Regina S.
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 8
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9856389	A1	19981217	WO 1998-US11737	19980605
W: AU, BR, CA, CN, JP, MX, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 6034074	A	20000307	US 1997-873010	19970611
CA 2293582	AA	19981217	CA 1998-2293582	19980605
AU 9878222	A1	19981230	AU 1998-78222	19980605
EP 983070	A1	20000308	EP 1998-926371	19980605
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.:

US 1997-873010	A	19970611
US 1996-713834	A2	19960913
WO 1998-US11737	W	19980605

ED Entered STN: 06 Jan 1999

AB Methods are provided for preventing the development of epithelial ovarian cancer by administering a Vitamin D compound in an amount capable of increasing apoptosis in non-neoplastic ovarian epithelial cells of the female subject.

IT **1406-16-2**, Vitamin D **1406-16-2D**, Vitamin D, derivs. **32222-06-3**, 1,25-Dihydroxyvitamin D3
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)

(vitamin D compds. for prevention of **ovarian** cancer)
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L88 ANSWER 23 OF 49 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:1006731 CAPLUS
DOCUMENT NUMBER: 142:17836
TITLE: Molecular activity of 1,25-dihydroxyvitamin D3 in primary cultures of human prostatic epithelial cells revealed by cDNA microarray analysis
AUTHOR(S): Peehl, Donna M.; Shinghal, Rajesh; Nonn, Larisa; Seto, Eugene; Krishnan, Aruna V.; Brooks, James D.; Feldman, David
CORPORATE SOURCE: Department of Urology, Stanford University School of Medicine, Stanford, CA, 94305, USA
SOURCE: Journal of Steroid Biochemistry and Molecular Biology (2004), 92(3), 131-141
CODEN: JSBBEZ; ISSN: 0960-0760
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 23 Nov 2004
AB 1,25-Dihydroxyvitamin D3 [1,25(OH)2D3] exerts anti-proliferative, differentiating and apoptotic effects on prostatic cells. These activities, in addition to epidemiol. findings that link Vitamin D to prostate cancer risk, support the use of 1,25(OH)2D3 for prevention or therapy of prostate cancer. The mol. mechanisms by which 1,25(OH)2D3 exerts antitumor effects on prostatic cells are not well-defined. In addition, there is heterogeneity among the responses of various prostate cell lines and primary cultures to 1,25(OH)2D3 with regard to growth inhibition, differentiation and apoptosis. To understand the basis of these differential responses and to develop a better model of Vitamin D action in the prostate, we performed cDNA microarray analyses of primary cultures of normal and malignant human prostatic epithelial cells, treated with 50 nM of 1,25(OH)2D3 for 6 and 24 h. CYP24 (25-hydroxyvitamin D3-24-hydroxylase) was the most highly upregulated gene. Significant and early upregulation of dual specificity phosphatase 10 (DUSP10), validated in five addnl. primary cultures, points to inhibition of members of the mitogen-activated protein kinase (MAPK) superfamily as a key event mediating activity of 1,25(OH)2D3 in prostatic epithelial cells. The functions of other regulated genes suggest protection by 1,25(OH)2D3 from oxidative stress. Overall, these results provide new insights into the mol. basis of antitumor activities of Vitamin D in prostate cells.
IT **32222-06-3**, 1,25-Dihydroxyvitamin D3
RL: BSU (Biological study, unclassified); **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(mol. activity of 1,25-dihydroxyvitamin D3 in primary cultures of human prostatic epithelial cells revealed by cDNA microarray anal.)
REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L88 ANSWER 24 OF 49 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:917645 CAPLUS
DOCUMENT NUMBER: 140:140007
TITLE: Genetic signatures of differentiation induced by 1α,25-dihydroxyvitamin D3 in human colon cancer cells
AUTHOR(S): Palmer, Hector G.; Sanchez-Carbayo, Marta; Ordonez-Moran, Paloma; Larriba, Maria Jesus;

Cordon-Cardo, Carlos; Munoz, Alberto
CORPORATE SOURCE: Instituto de Investigaciones Biomedicas "Alberto Sols", Consejo Superior de Investigaciones Cientificas-Universidad Autonoma de Madrid, Madrid, Spain
SOURCE: Cancer Research (2003), 63(22), 7799-7806
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 24 Nov 2003
AB Epidemiol. and preclin. data indicate that vitamin D and its most active metabolite 1α,25-dihydroxyvitamin D3 [1α,25(OH)2D3] have anticancer activity. Accordingly, clin. trials are under way using several nonhypercalcemic 1α,25(OH)2D3 analogs against various neoplasms including colon cancer. 1α,25(OH)2D3 induces proliferation arrest and epithelial differentiation of human SW480-ADH colon cancer cells. The authors examined the gene expression profiles associated with 1α,25(OH)2D3 exposure using oligonucleotide microarrays. 1α,25(OH)2D3 changed the expression levels of numerous previously unreported genes, including many involved in transcription, cell adhesion, DNA synthesis, apoptosis, redox status, and intracellular signaling. Most genes were up-regulated, and only a small fraction were down-regulated. Fourteen of 17 candidate genes studied were validated as 1α,25(OH)2D3 target genes by Northern and Western blotting or immunocytochem. They included c-JUN, JUNB, JUND, FREAC-1/FoxF1, ZNF-44/KOX7, plectin, filamin, keratin-13, G0S2, and the putative tumor suppressors NES-1 and protease M. There was little overlap between genes regulated after short (4 h) or long (48 h) exposure. Gene regulatory effects of 1α,25(OH)2D3 in SW480-ADH cells differed from those in LS-174T cells, which lack E-cadherin and do not differentiate in response to 1α,25(OH)2D3. Data from this study reveal that 1α,25(OH)2D3 causes a profound change in gene expression profiles and provide a mechanistic basis to the ongoing clin. studies using nonhypercalcemic vitamin D3 derivs. for colon cancer prevention and treatment.
IT **32222-06-3**, 1α,25-Dihydroxyvitamin D3
RL: BSU (Biological study, unclassified); **PAC (Pharmacological activity)**; BIOL (Biological study)
(genetic signatures of differentiation induced by 1α,25-dihydroxyvitamin D3 in human colon cancer cells)
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L88 ANSWER 25 OF 49 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2004230394 EMBASE
TITLE: Two 14-epi analogues of 1,25-dihydroxyvitamin D(3) protect human keratinocytes against the effects of UVB.
AUTHOR: De Haes P.; Garmyn M.; Verstuyf A.; De Clercq P.; Vandewalle M.; Vantieghem K.; Degreef H.; Bouillon R.; Segaert S.
CORPORATE SOURCE: R. Bouillon, Lab. for Exp. Med. and Endocrinology, Katholieke Universiteit Leuven, Gasthuisberg O and N9, Herestraat 49, 3000 Leuven, Belgium. roger.bouillon@med.kuleuven.ac.be
SOURCE: Archives of Dermatological Research, (2004) Vol. 295, No.

12, pp. 527-534.
Refs: 34
ISSN: 0340-3696 CODEN: ADMFAU
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 013 Dermatology and Venereology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040617
Last Updated on STN: 20040617

ABSTRACT: In search of photoprotective agents, we recently demonstrated a protective effect of 1,25-dihydroxyvitamin D(3) [1,25(OH)(2)D (3)] against different events mediated by ultraviolet B (UVB) in human keratinocytes. Pharmacological doses of 1,25(OH)(2)D(3) were required to obtain significant UVB protection; however, these doses cannot be used in vivo due to the calcemic properties of 1,25(OH)(2)D (3). Therefore, we evaluated the photoprotective capacities of two low-calcemic 14-epi analogues of 1,25(OH)(2)D(3), 19-nor-14-epi-23-yne-1,25(OH)(2)D(3) (TX 522) and 19-nor-14,20-bisepi-23-yne-1,25(OH)(2)D(3) (TX 527). Using cultured human keratinocytes, we investigated the influence of TX 522 and TX 527 on two hallmark events in UVB-irradiated keratinocytes: the induction of apoptosis and the production of interleukin-6 (IL-6). Treatment of the keratinocytes with TX 522 or TX 527, 24 h before irradiation, resulted in a significant and dose-dependent reduction of both UVB-induced apoptosis and IL-6 production. Both analogues were equally efficient in their anti-UVB effects and at least 100 times more potent than 1,25(OH)(2)D(3). We further demonstrated that metallothionein (MT) mRNA expression was clearly induced by 1,25(OH)(2)D(3) and both analogues. MT acts as a radical scavenger in oxygen-mediated UVB injury and its induction may therefore be relevant for the anti-UVB effects of 1,25(OH)(2)D(3) and both analogues. Taken together, these findings create new perspectives for the use of active vitamin D analogues as photoprotective agents.

CONTROLLED TERM: Medical Descriptors:
***keratinocyte**
*ultraviolet B radiation
radiation response
radiation dose
cell protection
in vivo study
cell culture
apoptosis
cytokine production
irradiation
concentration response
drug potency
human
normal human
controlled study
human cell
preschool child
article
priority journal
Drug Descriptors:
***calcitriol derivative: PD, pharmacology**
19 nor 14 epi 23 yne 1,25 dihydroxyvitamin d3: PD, pharmacology
19 nor 14,20 bisepi 23 yne 1,25 dihydroxyvitamin d3: PD, pharmacology

interleukin 6: EC, endogenous compound
metallothionein: EC, endogenous compound
messenger RNA: EC, endogenous compound
unclassified drug
tx 522
tx 527

CHEMICAL NAME: Tx 522; Tx 527

L88 ANSWER 26 OF 49 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2005060965 EMBASE
TITLE: Potentiation of cell killing by fractionated radiation and suppression of proliferative recovery in MCF-7 breast tumor cells by the Vitamin D(3) analog EB 1089.
AUTHOR: DeMasters G.A.; Gupta M.S.; Jones K.R.; Cabot M.; Wang H.; Gennings C.; Park M.; Bratland A.; Ree A.H.; Gewirtz D.A.
CORPORATE SOURCE: D.A. Gewirtz, Dept. Pharmacol./Toxicol. and Med., Virginia Commonwealth University, Medical College of Virginia, P.O. Box 980230, Richmond, VA 23298, United States. gewirtz@hsc.vcu.edu
SOURCE: Journal of Steroid Biochemistry and Molecular Biology, (2004) Vol. 92, No. 5, pp. 365-374.
Refs: 54
ISSN: 0960-0760 CODEN: JSBBEZ
PUBLISHER IDENT.: S 0960-0760(04)00378-4
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 014 Radiology
016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050218
Last Updated on STN: 20050218

ABSTRACT: A senescence-like growth arrest succeeded by recovery of proliferative capacity was observed in MCF-7 breast tumor cells exposed to fractionated radiation, 5 x 2 Gy. Exposure to EB 1089, an analog of the steroid hormone 1α, 25 dihydroxycholecalciferol (1α, 25 dihydroxy Vitamin D (3); calcitriol), prior to irradiation promoted cell death and delayed both the development of a senescent phenotype and the recovery of proliferative capacity. EB 1089 also reduced clonogenic survival over and above that produced by fractionated radiation alone and further conferred susceptibility to apoptosis in MCF-7 cells exposed to radiation. In contrast, EB 1089 failed to enhance the response to radiation (or to promote apoptosis) in normal breast epithelial cells or BJ fibroblast cells. EB 1089 treatment and fractionated radiation additively promoted ceramide generation and suppressed expression of polo-like kinase 1. Taken together, these data indicate that EB 1089 (and 1α, 25 dihydroxycholecalciferol or its analogs) could selectively enhance breast tumor cell sensitivity to radiation through the promotion of cell death, in part through the generation of ceramide and the suppression of polo-like kinase. .COPYRGT. 2004 Elsevier Ltd. All rights reserved.

CONTROLLED TERM: Medical Descriptors:
*cell killing
*cell proliferation
*radiation
cell strain MCF 7
phenotype

survival
apoptosis
breast epithelium
epithelium cell
fibroblast
human
controlled study
human cell
conference paper
Drug Descriptors:
***colecalciferol derivative: PD, pharmacology**
***seocalcitol: PD, pharmacology**
ceramide
polo like kinase 1
CAS REGISTRY NO.: (seocalcitol) 134404-52-7
CHEMICAL NAME: (1) Eb 1089
COMPANY NAME: (1) Leo Pharmaceuticals (Denmark)

L88 ANSWER 27 OF 49 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
ACCESSION NUMBER: 2004105827 EMBASE
TITLE: The role of the calcium-sensing receptor in cancer.
AUTHOR: Rodland K.D.
CORPORATE SOURCE: K.D. Rodland, Pacific Northwest National Lab., Biological Sciences Division, Richland, WA 99352, United States
SOURCE: Cell Calcium, (2004) Vol. 35, No. 3, pp. 291-295.
Refs: 47
ISSN: 0143-4160 CODEN: CECADV
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
005 General Pathology and Pathological Anatomy
016 Cancer
022 Human Genetics
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040318
Last Updated on STN: 20040318

ABSTRACT: The extracellular calcium-sensing receptor (CaR) is a versatile sensor of small, polycationic molecules ranging from Ca(2+) and Mg(2+) through polyarginine, spermine, and neomycin. The sensitivity of the CaR to changes in extracellular Ca(2+) over the range of 0.05-5 mM positions the CaR as a key mediator of cellular responses to physiologically relevant changes in extracellular Ca(2+). For many cell types, including intestinal epithelial cells, breast epithelial cells, keratinocytes, and ovarian surface epithelial cells, changes in extracellular Ca(2+) concentration over this range can switch the cellular behaviour from proliferation to terminal differentiation or quiescence. As cancer is predominantly a disease of disordered balance between proliferation, differentiation, and apoptosis, disruptions in the function of the CaR could contribute to the progression of neoplastic disease. Loss of the growth suppressing effects of elevated extracellular Ca(2+) have been demonstrated in parathyroid hyperplasias and in colon carcinoma, and have been correlated with changes in the level of CaR expression. Activation of the CaR has also been linked to increased expression and secretion of PTHrP (parathyroid hormone-related peptide), a primary causal factor in hypercalcemia of malignancy and a contributor to metastatic processes involving bone. Although mutation of the CaR does not appear to be an early event in carcinogenesis, loss or upregulation of normal CaR function can contribute to

several aspects of neoplastic progression, so that therapeutic strategies directed at the CaR could potentially serve a supportive function in cancer management.

CONTROLLED TERM: Medical Descriptors:
*carcinogenesis
*extracellular calcium
protein function
cell activity
cell type
intestine epithelium cell
breast epithelium
keratinocyte
ovary
cell proliferation
cell differentiation
apoptosis
disease activity
parathyroid hyperplasia: ET, etiology
colon carcinoma: DT, drug therapy
colon carcinoma: ET, etiology
colon carcinoma: PC, prevention
correlation analysis
protein induction
protein expression
hypercalcemia: ET, etiology
bone metastasis: ET, etiology
gene mutation
tumor growth
cancer therapy
human
nonhuman
article
priority journal
Drug Descriptors:
*calcium sensing receptor: DT, drug therapy
polycation: EC, endogenous compound
calcium ion: EC, endogenous compound
magnesium ion: EC, endogenous compound
polyarginine
spermine
neomycin
parathyroid hormone related protein: EC, endogenous compound
calcium derivative: CB, drug combination
calcium derivative: DT, drug therapy
vitamin D: CB, drug combination
vitamin D: DT, drug therapy

CAS REGISTRY NO.: (calcium ion) 14127-61-8; (magnesium ion) 22537-22-0; (polyarginine) 24937-47-1, 25212-18-4, 26700-68-5; (spermine) 306-67-2, 71-44-3; (neomycin) 11004-65-2, 1404-04-2, 1405-10-3, 8026-22-0

L88 ANSWER 28 OF 49 EMBASE
on STN

ACCESSION NUMBER: 2003007741 EMBASE

TITLE: Ursodeoxycholic acid and F(6)-D(3) inhibit aberrant crypt proliferation in the rat azoxymethane model of colon cancer: Roles of cyclin D1 and E-cadherin.

AUTHOR: Wali R.K.; Khare S.; Tretiakova M.; Cohen G.; Nguyen L.;

Hart J.; Wang J.; Wen M.; Ramaswamy A.; Joseph L.; Sitrin M.; Brasitus T.; Bissonnette M.
CORPORATE SOURCE: M. Bissonnette, Department of Medicine, MC 4076, Univ. of Chicago Hospitals/Clinics, 5841 South Maryland Avenue, Chicago, IL 60637, United States.
mbissonn@medicine.bsd.uchicago.edu
SOURCE: Cancer Epidemiology Biomarkers and Prevention, (1 Dec 2002) Vol. 11, No. 12, pp. 1653-1662.
Refs: 61
ISSN: 1055-9965 CODEN: CEBPE4
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20030129
Last Updated on STN: 20030129

ABSTRACT: We have previously demonstrated that ursodeoxycholic acid (UDCA) and a fluorinated analogue of vitamin D(3), F(6)-D(3), inhibited colonic carcinogenesis in the azoxymethane (AOM) model. Generalized colonic mucosal hyperproliferation and aberrant crypt foci (ACF) are intermediate biomarkers of colon cancer. Using these biomarkers, in this study we examined the anticarcinogenic mechanisms of these chemopreventive agents. Rats were maintained on AIN-76A chow or supplemented with 0.4% UDCA or F(6)-D(3) (2.5 nmol/kg chow) and treated weekly with AOM 20 mg i.p./kg wt or saline x 2 weeks. F(6)-D(3) was continued for an additional 2 weeks and UDCA for the duration of the study. At 40 weeks, animals received bromodeoxyuridine (BrdUrd) i.p. 2 h before sacrifice. A portion of each tumor was fixed in formalin and the remainder flash frozen. Colons were divided longitudinally and half-fixed in formalin and half in ethanol. The size and location of methylene bluestained ACF were recorded. Cell proliferation (BrdUrd labeling) and apoptosis (terminal deoxynucleotidyl transferase-mediated nick end labeling assay) were measured in colonic crypts and tumors. Protein expression levels of several regulators of cell proliferation were analyzed by immunostaining and Western blotting. Colonic crypt cyclin D1 and E-cadherin mRNA levels were measured by real-time PCR. In saline injected controls, neither UDCA nor F(6)-D(3) alone had any effect on cytokinetic parameters or on the expression of mitogenic regulators. AOM significantly increased the proliferation (percentage of BrdUrd-positive cells) of both ACF (23.1 ± 1.7%) and non-ACF crypts (17.6 ± 1.6%), compared with normal colonic crypts (4.5 ± 0.8%; $P < 0.05$). This hyperproliferation was accompanied by a 5-fold increase in cyclin D1 and >50% decrease in E-cadherin protein ($P < 0.05$) in ACF, both of which are predicted to be growth-enhancing alterations. UDCA and F(6)-D(3) significantly ($P < 0.05$) inhibited AOM-induced crypt cell hyperproliferation, ACF development, and tumor burden. These chemopreventive agents also significantly blocked AOM-induced alterations in cyclin D1 and E-cadherin protein in ACF and tumors. In ACF, changes in mRNA levels of cyclin D1, but not E-cadherin, paralleled alterations in protein expression. Cyclooxygenase-2 and inducible nitric oxide synthase were increased in AOM tumors but not in ACF, and these changes were blocked by UDCA and F(6)-D(3). UDCA and F(6)-D(3) significantly inhibited ACF development and hyperproliferation, in part, by preventing carcinogen-induced alterations in cyclin D1 and E-cadherin. In established tumors, UDCA and F(6)-D(3) also limited inductions of cyclooxygenase-2 and inducible nitric oxide synthase, which together with their effects on cyclin D1 and E-cadherin, contribute to their chemopreventive actions.

CONTROLLED TERM: Medical Descriptors:
*colon cancer: DT, drug therapy

*colon cancer: PC, prevention
***crypt cell**
cell proliferation
fluorination
colon carcinogenesis
colon mucosa
drug mechanism
antineoplastic activity
chemoprophylaxis
protein expression
protein content
immunohistochemistry
Western blotting
cell kinetics
enzyme induction
apoptosis
nonhuman
male
rat
animal experiment
animal model
controlled study
animal tissue
article
priority journal
Drug Descriptors:
*ursodeoxycholic acid: CB, drug combination
*ursodeoxycholic acid: DT, drug therapy
*ursodeoxycholic acid: PD, pharmacology
*ursodeoxycholic acid: PO, oral drug administration
*colecalciferol derivative: CB, drug combination
***colecalciferol derivative: DT, drug therapy**
***colecalciferol derivative: PD, pharmacology**
*colecalciferol derivative: PO, oral drug administration
*1alpha,25 dihydroxy 16 ene 23 yne 26,27 hexafluorocholecalciferol: CB, drug combination
*1alpha,25 dihydroxy 16 ene 23 yne 26,27 hexafluorocholecalciferol: DT, drug therapy
*1alpha,25 dihydroxy 16 ene 23 yne 26,27 hexafluorocholecalciferol: PD, pharmacology
*1alpha,25 dihydroxy 16 ene 23 yne 26,27 hexafluorocholecalciferol: PO, oral drug administration
*cyclin D1: EC, endogenous compound
*uvomorulin: EC, endogenous compound
biological marker: EC, endogenous compound
broxuridine
methylene blue
messenger RNA: EC, endogenous compound
cyclooxygenase 2: EC, endogenous compound
nitric oxide synthase: EC, endogenous compound
sodium chloride
azoxymethane
unclassified drug

CAS REGISTRY NO.: (ursodeoxycholic acid) 128-13-2, 2898-95-5; (uvomorulin) 112956-45-3; (broxuridine) 59-14-3; (methylene blue) 61-73-4; (nitric oxide synthase) 125978-95-2; (sodium chloride) 7647-14-5; (azoxymethane) 25843-45-2

COMPANY NAME: Hoffmann La Roche (United States)

L88 ANSWER 29 OF 49 EMBASE

on STN

ACCESSION NUMBER: 2002095175 EMBASE
TITLE: Effect of vitamin D(3) on the increased expression of bcl-x(L) in psoriasis.
AUTHOR: Fukuya Y.; Higaki M.; Higaki Y.; Kawashima M.
CORPORATE SOURCE: M. Higaki, Institute of Medical Science, St. Marianna Medical School, 2-16-1 Sugao, Miyamae-ku, Kawasaki, Kanagawa 216-0015, Japan. megumu@dd.iij4u.or.jp
SOURCE: Archives of Dermatological Research, (2001) Vol. 293, No. 12, pp. 620-625.
Refs: 25
ISSN: 0340-3696 CODEN: ADMFAU
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
013 Dermatology and Venereology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20020321
Last Updated on STN: 20020321

ABSTRACT: Psoriasis is a chronic skin disease characterized by epidermal hyperproliferation, which may be regulated by several mechanisms including apoptosis. In this study, we detected DNA fragmentation by the terminal deoxynucleotide transferase-mediated dUTP nick-end labeling (TUNEL) method and immunohistochemically examined the expression of Bcl-x and Bax in psoriasis. We determined the expression of bcl-x(L) mRNA by RT-PCR, and also determined the effect of vitamin D(3) (VD3) on bcl-x(L) mRNA expression in cultured normal human keratinocytes by RT-PCR, and the expression of Bcl-x(L) in psoriatic lesions before and after topical application of VD3. A large number of TUNEL-positive cells as well as Bcl-x(L)- and Bax-positive cells were observed throughout the epidermis in psoriatic lesions. Whereas, in nonlesional and normal skin, only a few TUNEL-positive cells were observed and only the lower epidermis showed positive staining for Bcl-x and Bax. We also observed higher expression of bcl-x(L) mRNA in psoriatic lesions than in nonlesional and normal skin. The expression of bcl-xL mRNA in cultured normal human keratinocytes stimulated or not with IFN-γ and PMA was suppressed by VD3 in a dosedependent manner, and the expression of Bcl-x(L), but not Bax, in psoriatic lesional skin decreased after topical application of VD3 for 4 weeks. In conclusion, it is suggested that the apoptotic process in psoriatic lesions is in part regulated by Bcl-x(L), and decreasing the expression of Bcl-x(L) by treatment with VD3 might ameliorate psoriatic lesions by contributing to the completion of the apoptotic process.

CONTROLLED TERM: Medical Descriptors:
*psoriasis: DT, drug therapy
nick end labeling
immunohistochemistry
protein expression
gene expression
reverse transcription polymerase chain reaction
drug effect
keratinocyte
cell culture
dose response
apoptosis
cell stimulation
drug mechanism
human

Searched by Barb O'Bryen, STIC 2-2518

male
female
clinical article
controlled study
human tissue
human cell
aged
adult
article
priority journal
Drug Descriptors:
***colecalciferol: DT, drug therapy**
***colecalciferol: PD, pharmacology**
*colecalciferol: TP, topical drug administration
*protein bcl xl: EC, endogenous compound
messenger RNA: EC, endogenous compound
gamma interferon
DNA fragment: EC, endogenous compound
protein Bax: EC, endogenous compound
CAS REGISTRY NO.: (colecalciferol) 1406-16-2, 67-97-0; (protein bcl xl) 151033-38-4; (gamma interferon) 82115-62-6

L88 ANSWER 30 OF 49 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED.
on STN DUPLICATE 15
ACCESSION NUMBER: 2001-0307999 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 2001 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): An assessment of the evidence linking calcium and **vitamin D** to colon cancer prevention
AUTHOR: PARODI Peter W.
CORPORATE SOURCE: Human Nutrition Program, Dairy Research and Development Corporation, Level 3, 84 William Street, Melbourne, Victoria 3000, Australia
SOURCE: Australian Journal of Dairy Technology, (2001), 56(1), 38-58, refs. 4 p.1/4
ISSN: 0004-9433 CODEN: AJDTAZ
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: Australia
LANGUAGE: English
AVAILABILITY: INIST-8857, 354000098163990080
ABSTRACT: Colorectal cancer is a common form of cancer in both men and women. This review assesses the evidence that calcium and **vitamin D** protect against colorectal cancer. Although cellular and extracellular calcium levels may be important in carcinogenesis, it is the role of dietary calcium in colonic lumen physiology that has attracted the most attention. Dietary and diet-induced components such as long chain fatty acids and bile acids, which are present in the faecal stream, can be cytotoxic to colonic **epithelial** cells. Damaged cells area removed by **apoptosis.** Replacement of these cells causes an increase in the cellular proliferation rate that increases the risk of mutations in oncogenes and tumor suppressor genes, and thus subsequent colorectal cancer. The **chemopreventive** action of calcium results from the formation of non-toxic insoluble complexes with the cytotoxic lipids. Most animal studies show that dietary calcium

can decrease the incidence of chemically induced or bile-acid-promoted cellular proliferation, preneoplastic lesions and colon tumors. However, conflicting results are common with human studies that explore the association between calcium intake and the risk of colorectal adenoma or carcinoma. Although the majority of the studies have demonstrated an inverse association, most did riot attain statistical significance. Human intervention studies, where supplemental calcium was used to reduce colonic cell proliferation rate, have also produced conflicting results. This intervention appears to be effective when the initial proliferation rates are high but not when they are normal. There is also limited evidence that calcium supplementation can prevent the recurrence of adenomas in patients who had previously had adenomas resected. **Vitamin D** .sub.3 can likewise help prevent colorectal carcinoma in animals and humans. Moreover, of considerable significance are the studies that suggest **vitamin D** deficiency can attenuate the beneficial effect of calcium. In this review, reasons for the conflicting outcomes in the various studies are explored in terms of a range of individual, cultural and lifestyle factors. Recent evidence suggests that the effect of calcium on colorectal cancer risk differs according to the molecular nature of the mutated gene. Evaluation of specific types of mutations will need to be included in future studies.

CLASSIFICATION CODE: 002B04D07; Life sciences; Medical sciences; Oncology; Experimental tumor; Gastroenterology, Digestive system
002A35A01; Life sciences; Biological sciences; Agriculture, Food industry

CONTROLLED TERM: Diet; **Vitamin D**; Malignant tumor; Prevention; Review; Calcium; Colon

BROADER TERM: Macronutrient(mineral); Digestive system

L88 ANSWER 31 OF 49 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED. on STN DUPLICATE 21

ACCESSION NUMBER: 1999-0172947 PASCAL

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TITLE (IN ENGLISH): **Vitamin D** analogue EB1089-induced prostate regression is associated with increased gene expression of insulin-like growth factor binding proteins

AUTHOR: NICKERSON T.; HUYNH H.

CORPORATE SOURCE: Lady Davis Institute for Medical Research, McGill University, 3755 Cote Ste Catherine Road, Montreal, Quebec, H3T 1E2, Canada

SOURCE: Journal of endocrinology, (1999), 160(2), 223-229, 39 refs.
ISSN: 0022-0795 CODEN: JOENAK

DOCUMENT TYPE: Journal

BIBLIOGRAPHIC LEVEL: Analytic

COUNTRY: United Kingdom

LANGUAGE: English

AVAILABILITY: INIST-1094, 354000074236930070

ABSTRACT: **Vitamin D** analogues have an

antiproliferative effect on prostate cancer cells in vitro and thus have been proposed as candidates for **chemoprevention** of prostate cancer.
Insulin-like growth factor (IGF)-I has been shown to protect cells front **apoptosis** and plays an essential role in normal prostate physiology. We have studied the effects of the 1,25-**dihydroxyvitamin D**.sub.3 analogue EB1089 on the IGF system in the prostate in vivo, Treatment of rats with EB1089 for 14 days caused a 25% decrease in ventral prostate weight. **Apoptosis** was detected in prostate sections of EB1089-treated rats by terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNE L) assay and histologic examination of hematoxylin/ eosin stained tissue sections indicated that secretory **epithelial** cells were flattened, a characteristic of cells undergoing pressure-induced atrophy, Ventral prostate regression was associated with 15- to 25-fold increases in gene expression of IGF-binding proteins (IGFBPs)-2,-3,-4 and-5. We also observed a 40-fold increase in prostatic IGF-I mRNA levels in response to EB1089. Although we have previously shown that castration of rats leads to upregulation of IGFBPs in the ventral prostate, EB1089 treatment had no effect on serum levels of dihydrotestosterone or free testosterone. These results suggest that prostate regression induced by EB1089 may be related to alterations in availability of IGF-I as a result of increased production of IGFBPs.

CLASSIFICATION CODE: 002B02O; Life sciences; Medical sciences; Pharmacology; Endocrinology, Endocrine disorders

CONTROLLED TERM: **Cholecalciferol**(1,25-dihydroxy); Prostate; Analog; Insulin like growth factor binding protein; Mechanism of action; Gene expression; Rat; Antineoplastic agent

BROADER TERM: **Vitamin D**; Steroid hormone; Urogenital system; Rodentia; Mammalia; Vertebrata

L88 ANSWER 32 OF 49 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED. on STN DUPLICATE 23

ACCESSION NUMBER: 1998-0481662 PASCAL

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TITLE (IN ENGLISH): **Chemoprevention** of colorectal cancer

AUTHOR: LANGMAN M.; BOYLE P.

CORPORATE SOURCE: Department of Medicine, Queen Elizabeth Hospital, Birmingham B15 2TH, United Kingdom; Division of Epidemiology and Biostatistics, European Institute of Oncology, via Ripamonti 435, 20141 Milan, Italy

SOURCE: Gut, (1998), 43(4), 578-585, 118 refs.
ISSN: 0017-5749 CODEN: GUTTAK

DOCUMENT TYPE: Journal

BIBLIOGRAPHIC LEVEL: Analytic

COUNTRY: United Kingdom

LANGUAGE: English

AVAILABILITY: INIST-1722, 354000071224440290

ABSTRACT: Colorectal cancer is the fourth commonest form of cancer in men with 678 000 estimated new cases per year worldwide, representing 8.9% of all new cancers.

The disease is most frequent in Occidental countries and particularly so in North America, Australia, New Zealand, and parts of Europe. Prospects for colorectal cancer control are bright and a number of possible approaches could prove fruitful. Among these, pharmaceutical measures seem to be valid and logical approaches to the prevention of colorectal cancer and diminishing its impact. Such approaches could concentrate in primary prevention in at-risk subjects or be applied in altering the course of precursor or established disease. Treatments used must fulfil basic requirements of biological plausibility and safety in continued use in large numbers of subjects. Those available include vitamins and minerals, and other drugs with potential as antioxidants, immune modulators or promoters of cell differentiation or **apoptosis**. Of the various regimens suggested, vitamin A supplementation may even predispose to adverse outcomes, and antioxidant vitamins in general have no coherent body of evidence to support their use. N-acetylcysteine and ursodeoxycholic acid have promising characteristics but there are as yet no clinical data to support the use of the former in gut **epithelial** cancer, and formal dose ranging studies must be carried out before the latter is submitted to large scale trial. Folate shows promising characteristics but non-steroidal anti-inflammatory drugs and **vitamin D** seem the most promising agents. Both seem to reduce the incidence of disease, and to reduce growth rates and/or induce differentiation or **apoptosis** in gut **epithelial** cancer cells. Both are also well understood pharmacologically. They may be preferred to newer selective compounds in the same class until these newer compounds are confirmed as safe for widespread long term use.

CLASSIFICATION CODE: 002B02H; Life sciences; Medical sciences; Pharmacology; Gastroenterology, Digestive system

CONTROLLED TERM: Carcinoma; Colon; Rectum; **Chemoprophylaxis**; Non steroidal antiinflammatory agent; Retinol; Ascorbic acid; **Vitamin D**; α-Tocopherol; Folate; Calcium; Ursodeoxycholic acid; Antihistaminic; Review; Human

BROADER TERM: Malignant tumor; Digestive diseases; Intestinal disease; Colonic disease; Rectal disease

L88 ANSWER 33 OF 49 on STN PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED.

ACCESSION NUMBER: 2004-0374670 PASCAL

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TITLE (IN ENGLISH): Pathways mediating the growth-inhibitory actions of **Vitamin D** in prostate cancer
Nutritional genomics and proteomics in cancer prevention

AUTHOR: PEEHL Donna M.; KRISHNAN Aruna V.; FELDMAN David KIM Young S. (ed.); MILNER John A. (ed.)

CORPORATE SOURCE: Department of Urology, Stanford University School of Medicine, Stanford, CA 94305, United States; Department of Medicine, Stanford University School of

Medicine, Stanford, CA 94305, United States
Nutritional Science Research Group, Division of Cancer Prevention, National Cancer Institute, Bethesda, MD, United States
National Cancer Institute. Center for Cancer Research, United States (patr.); National Cancer Institute. Division of Cancer Prevention, United States (patr.); National Institutes of Health. National Center for Complementary and Alternative Medicine, United States (patr.); National Institutes of Health. Office of Dietary Supplements, United States (patr.); National Institutes of Health. Office of Rare Diseases, United States (patr.); American Society for Nutritional Sciences, United States (patr.)

SOURCE: The Journal of nutrition, (2003), 133(7, SUP), 2461S-2469S, 109 refs.
Conference: Nutritional genomics and proteomics in cancer prevention. Conference, Bethesda, MD (United States), 5 Sep 2002
ISSN: 0022-3166 CODEN: JONUAI
DOCUMENT TYPE: Journal; Conference
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United States
LANGUAGE: English
AVAILABILITY: INIST-2042, 354000119919250110

ABSTRACT: **Vitamin D** is emerging as an important dietary factor that affects the incidence and progression of many malignancies including prostate cancer. The active form of **vitamin D**, 1,25-dihydroxycholecalciferol [1,25(OH).sub.2D.sub.3], inhibits the growth and stimulates the differentiation of prostate cancer cells. We have studied primary cultures of normal and cancer-derived prostatic **epithelial** cells as well as established human prostate cancer cell lines to elucidate the molecular pathways of 1,25(OH).sub.2D.sub.3 actions. These pathways are varied and appear to be cell specific. In LNCaP cells, 1,25(OH).sub.2D.sub.3 mainly causes growth arrest through the induction of insulin-like growth factor binding protein-3 and also stimulates **apoptosis** to a much smaller extent. We have used cDNA-microarray analyses to identify additional genes that are regulated by 1,25(OH).sub.2D.sub.3 and to raise novel therapeutic targets for use in the **chemoprevention** or treatment of prostate cancer. Less calcemic analogs of 1,25(OH).sub.2D.sub.3 that have more antiproliferative activity are being developed that will be more useful clinically. In target cells, 1,25(OH).sub.2D.sub.3 induces 24-hydroxylase, the enzyme that catalyzes its self inactivation. Cotreatment with 24-hydroxylase inhibitors enhances the antiproliferative activity of 1,25(OH).sub.2D.sub.3. The combination of other anticancer agents such as retinoids with **vitamin D** offers another promising therapeutic approach. A small clinical trial has shown that 1,25(OH).sub.2D.sub.3 can slow the rate of prostate-specific antigen increase in prostate cancer patients, which demonstrates proof of the concept that

vitamin D or its analogs are clinically effective. Our research is directed at understanding the mechanisms of **vitamin D** action in prostate cells with the goal of developing **chemoprevention** and treatment strategies to improve prostate cancer therapy.

CLASSIFICATION CODE: 002A16E; Life sciences; Biological sciences; Vertebrates physiology

CONTROLLED TERM: Growth; **Vitamin D**; Analog; Biological receptor; Hydroxylase; Gene; Prostate cancer

BROADER TERM: Oxidoreductases; Enzyme; Male genital diseases; Urinary system disease; Malignant tumor; Prostate disease

L88 ANSWER 34 OF 49 PASCAL COPYRIGHT 2005 INIST-CNRS. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2004-0374715 PASCAL

TITLE (IN ENGLISH): **Vitamin D**-3 receptor as a target for breast cancer prevention
Nutritional genomics and proteomics in cancer prevention

AUTHOR: WELSH Joellen; WIETZKE Jennifer A.; ZINSER Glendon M.; BYRNE Belinda; SMITH Kelly; NARVAEZ Carmen J. KIM Young S. (ed.); MILNER John A. (ed.)

CORPORATE SOURCE: Department of Biological Sciences, University of Notre Dame, Notre Dame, IN 46556, Canada
Nutritional Science Research Group, Division of Cancer Prevention, National Cancer Institute, Bethesda, MD, United States
National Cancer Institute. Center for Cancer Research, United States (patr.); National Cancer Institute. Division of Cancer Prevention, United States (patr.); National Institutes of Health. National Center for Complementary and Alternative Medicine, United States (patr.); National Institutes of Health. Office of Dietary Supplements, United States (patr.); National Institutes of Health. Office of Rare Diseases, United States (patr.); American Society for Nutritional Sciences, United States (patr.)

SOURCE: The Journal of nutrition, (2003), 133(7, SUP), 2425S-2433S, 63 refs.
Conference: Nutritional genomics and proteomics in cancer prevention. Conference, Bethesda, MD (United States), 5 Sep 2002
ISSN: 0022-3166 CODEN: JONUAI

DOCUMENT TYPE: Journal; Conference

BIBLIOGRAPHIC LEVEL: Analytic

COUNTRY: United States

LANGUAGE: English

AVAILABILITY: INIST-2042, 354000119919250050

ABSTRACT: The **vitamin D**-3 receptor (VDR) is a nuclear receptor that modulates gene expression when complexed with its ligand 1-a,25-dihydroxycholecalciferol [1,25(OH).sub.2-D.sub.3], which is the biologically active form of **vitamin D**-3. The cellular effects of VDR signaling include growth arrest, differentiation

and/or induction of **apoptosis**, which indicate that the **vitamin D** pathway participates in negative-growth regulation. Although much attention has been directed in recent years toward the development of synthetic **vitamin D** analogs as therapeutic agents for a variety of human cancers including those derived from the mammary gland, studies on **vitamin D** as a **chemopreventive** agent for breast cancer have been quite limited. The VDR is expressed in normal mammary gland, where it functions to oppose estrogen-driven proliferation and maintain differentiation; this suggests that 1,25(OH).sub.2-D.sub.3 participates in negative-growth regulation of mammary **epithelial** cells. Furthermore, preclinical studies show that **vitamin D** compounds can reduce breast cancer development in animals, and human data indicate that both **vitamin D** status and genetic variations in the VDR may affect breast cancer risk. Collectively, findings from cellular, molecular and population studies suggest that the VDR is a nutritionally modulated growth-regulatory gene that may represent a molecular target for **chemoprevention** of breast cancer.

CLASSIFICATION CODE: 002A16E; Life sciences; Biological sciences; Vertebrates physiology

CONTROLLED TERM: **Vitamin D**; Biological receptor; Prevention; Mammary gland; Mutation; Animal; Malignant tumor; Mouse; Breast cancer

BROADER TERM: Mammary gland diseases; Rodentia; Mammalia; Vertebrata

L88 ANSWER 35 OF 49 on STN PASCAL

ACCESSION NUMBER: 2003-0225689 PASCAL

TITLE (IN ENGLISH): **Chemoprevention** of mammary carcinogenesis by 1α- **hydroxyvitamin D**.sub.5, a synthetic analog of **Vitamin D**
Dietary and Medicinal Antimutagens and Anticarcinogens: Molecular Mechanisms and **Chemopreventive** Potential

AUTHOR: MEHTA Rajendra G.; HUSSAIN Erum A.; MEHTA Rajeshwari R.; DAS GUPTA Tapas K.
SURTH Young-Joon (ed.); FERGUSON Lynnette R. (ed.)

CORPORATE SOURCE: Department of Surgical Oncology, College of Medicine, University of Illinois at Chicago, 840 South Wood Street (M/C 820), Chicago, IL 60612, United States
College of Pharmacy, Seoul National University, Shimlin-dong, Dwanak-gu, Seoul 151-742, Korea, Republic of; Department of Nutrition/ACSRC, The University of Auckland, Private Bag 92019, Auckland, New Zealand
Korean Environmental Mutagen Society, Korea, Republic of (patr.); Korean Society of Toxicology, Korea, Republic of (patr.); Korea Food and Drug Administration, Korea, Republic of (patr.)

SOURCE: Mutation research. Fundamental and molecular

mechanisms of mutagenesis, (2003), 523-24, 253-264, 38 refs.
Conference: Meeting on Dietary and Medicinal Antimutagens and Anticarcinogens: Molecular Mechanisms and Chemopreventive Potential, Seoul (Korea, Republic of), 17 Oct 2001
ISSN: 1386-1964
DOCUMENT TYPE: Journal; Conference
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: Netherlands
LANGUAGE: English
AVAILABILITY: INIST-12206A, 354000110736820250
ABSTRACT: Numerous analogs of **Vitamin D** have been synthesized in recent years with the hope of generating a compound that retains the anticarcinogenic activity of **Vitamin D** without causing any toxicity. We synthesized such an analog, 1a-hydroxy-24-ethylcholecalciferol [1α- **hydroxyvitamin D**.sub.5 or 1α(OH)D.sub.5], and showed that it was tolerated by rats and mice at a much higher dose than 1α,25 dihydroxy **cholecalciferol** [1α,25(OH).sub.2D.sub.3]. This property makes it a prime candidate for **chemoprevention** studies. In the mouse mammary gland organ culture (MMOC), 1α(OH)D.sub.5 inhibited carcinogen-induced development of both mammary alveolar and ductal lesions. In vivo carcinogenesis study showed statistically significant reduction of tumor incidence and multiplicity in N-methyl-N-nitrosourea (MNU)-treated rats that were fed 25-50 μg 1α(OH)D.sub.5/kg diet. There were no adverse effects on plasma calcium concentrations. In order to determine if the effect of 1α(OH)D.sub.5 would be selective in suppressing proliferation of transformed cells, its effects on cell growth and proliferation were compared between BT474 (cancer) and MCF12F (non-tumorigenic) human breast **epithelial** cells. Results showed that 1α(OH)D.sub.5 induced **apoptosis** and cell cycle G1 phase arrest in BT474 breast cancer cells without having any effects on proliferation of the MCF12F cells. In addition, in MMOC it had no growth inhibitory effects on normal **epithelial** cell proliferation in the absence of carcinogen. Similarly, non-tumorigenic human breast **epithelial** cells in explant culture did not respond to 1α(OH)D.sub.5, whereas treatment with 1α(OH)D.sub.5 induced **cell death** in the explants of cancer tissue. These results collectively indicate that 1α(OH)D.sub.5 selectively induced **apoptosis** only in transformed cells but not in normal breast **epithelial** cells. Interestingly, the growth inhibitory effects of 1α(OH)D.sub.5 were observed in **Vitamin D** receptor positive (VDR.sup.+) breast cancer cells, but not in highly metastatic VDR- breast cancer cells, such as MDA-MB-435 and MDA-MB-231, suggesting that 1α(OH)D.sub.5 action may be mediated, in part,

by VDR.
CLASSIFICATION CODE: 002A04H04; Life sciences; Biological sciences; Cell biology, Cell physiology; Oncology
CONTROLLED TERM: Cell line; Rat; Mouse; Human; Carcinogenesis; **Vitamin D**; Analog; Anticarcinogen; Prevention; Chemotherapy; Malignant tumor; Breast disease
BROADER TERM: Rodentia; Mammalia; Vertebrata

L88 ANSWER 36 OF 49 on STN PASCAL
ACCESSION NUMBER: 2004-0022155 PASCAL

TITLE (IN ENGLISH): New insights regarding pharmacologic approaches for **ovarian** cancer prevention
Current Topics in **Ovarian** Cancer
AUTHOR: RODRIGUEZ Gustavo
DISIS Mary L. (ed.)
CORPORATE SOURCE: Department of Obstetrics and Gynecology, Northwestern University, Feinberg School of Medicine, Chicago, IL, United States; Division of Gynecologic Oncology, evanston Northwestern Healthcare, Evanston, IL, United States
Department of Oncology, University of Washington, 1959 NE Pacific Street, HSB 1321, Box 356537, Seattle, WA 98195-6527, United States
SOURCE: Hematology/oncology clinics of North America, (2003), 17(4), x, 1007-1020 [15 p.], 82 refs.
ISSN: 0889-8588 CODEN: HCNAEQ
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United States
LANGUAGE: English
AVAILABILITY: INIST-21432, 354000112712520080
ABSTRACT: The pathogenesis of **epithelial ovarian** cancer is not completely understood, but it commonly is believed that the process of recurrent ovulation (incessant ovulation) causes genetic damage in **ovarian epithelial** cells and that sufficient genetic damage can lead to **ovarian** cancer in susceptible individuals. Under this model, it has been suggested that reproductive and hormonal factors, such as pregnancy and oral contraceptive use, decrease **ovarian** cancer risk mainly via their inhibitory effects on ovulation. There is mounting evidence that the **ovarian epithelium** is a hormonally responsive target organ whose biology can be impacted strongly by the local hormonal environment. Progestin-mediated **apoptotic** effects may be a major mechanism underlying the **ovarian** cancer protective effects of pregnancy (a high progestin state) and oral contraceptive pill use. Similarly, retinoids, **vitamin D**, and non-steroidal anti-inflammatory drugs may have biologic effects on the **ovarian epithelium** that are cancer preventive, whereas androgens may have stimulatory effects on the **ovarian epithelium**, leading to an

increased **ovarian** cancer risk.
CLASSIFICATION CODE: 002B20C02; Life sciences; Medical sciences; Gynecology, Genital system; Oncology
CONTROLLED TERM: Malignant tumor; **Ovary**; Human; Prevention; Hormone replacement therapy; **Vitamin D**; Non steroidal antiinflammatory agent; Retinoid; Treatment; Chemotherapy; Treatment efficiency; Risk factor; Toxicity; Review; **Epithelium**
BROADER TERM: Female genital diseases; **Ovarian** diseases

L88 ANSWER 37 OF 49 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 2003:36828855 BIOTECHNO
TITLE: Pathways mediating the growth-inhibitory actions of **vitamin D** in prostate cancer
AUTHOR: Peehl D.M.; Krishnan A.V.; Feldman D.
CORPORATE SOURCE: D. Feldman, Department of Medicine, Stanford Univ. School of Medicine, Stanford, CA 94305, United States. E-mail: feldman@cmgm.stanford.edu
SOURCE: Journal of Nutrition, (01 JUL 2003), 133/7 SUPPL. (2461S-2469S), 109 reference(s)
CODEN: JONUAI ISSN: 0022-3166
DOCUMENT TYPE: Journal; Conference Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT: **Vitamin D** is emerging as an important dietary factor that affects the incidence and progression of many malignancies including prostate cancer. The active form of **vitamin D**, 1,25-dihydroxycholecalciferol [1,25(OH).sub.2D.sub.3], inhibits the growth and stimulates the differentiation of prostate cancer cells. We have studied primary cultures of normal and cancer-derived prostatic **epithelial** cells as well as established human prostate cancer cell lines to elucidate the molecular pathways of 1,25(OH).sub.2D.sub.3 actions. These pathways are varied and appear to be cell specific. In LNCaP cells, 1,25(OH).sub.2D.sub.3 mainly causes growth arrest through the induction of insulin-like growth factor binding protein-3 and also stimulates **apoptosis** to a much smaller extent. We have used cDNA-microarray analyses to identify additional genes that are regulated by 1,25(OH).sub.2D.sub.3 and to raise novel therapeutic targets for use in the **chemoprevention** or treatment of prostate cancer. Less calcemic analogs of 1,25(OH).sub.2D.sub.3 that have more antiproliferative activity are being developed that will be more useful clinically. In target cells, 1,25(OH).sub.2D.sub.3 induces 24-hydroxylase, the enzyme that catalyzes its self inactivation. Cotreatment with 24-hydroxylase inhibitors enhances the antiproliferative activity of 1,25(OH).sub.2D.sub.3. The combination of other anticancer agents such as retinoids with **vitamin D** offers another promising therapeutic approach. A small clinical trial has shown that 1,25(OH).sub.2D.sub.3 can slow the rate of prostate-specific antigen increase in prostate cancer

patients, which demonstrates proof of the concept that **vitamin D** or its analogs are clinically effective. Our research is directed at understanding the mechanisms of **vitamin D** action in prostate cells with the goal of developing **chemoprevention** and treatment strategies to improve prostate cancer therapy.

CONTROLLED TERM: *cancer growth; *prostate cancer; *growth inhibition; ***vitamin D** metabolism; *vitamin supplementation; ***vitamin D**; * **calcitriol**; *prostate specific antigen; dietary intake; incidence; disease course; cell differentiation; molecular biology; cell specificity; DNA microarray; gene identification; gene targeting; drug activity; catalysis; enzyme inactivation; side effect; human; nonhuman; clinical trial; controlled study; human cell; animal cell; conference paper; somatomedin binding protein 3; enzyme inhibitor; 24 hydroxylase inhibitor; complementary DNA; antineoplastic agent; retinoid; retinoic acid; alitretinoin; **vitamin D** derivative; ro 24 5531; platinum derivative; paclitaxel; suramin; hydrocortisone; genistein; unclassified drug

CAS REGISTRY NUMBER: (**calcitriol**) **32222-06-3**, **32511-63-0**, 66772-14-3; (retinoic acid) 302-79-4; (alitretinoin) 5300-03-8; (paclitaxel) 33069-62-4; (suramin) 129-46-4, 145-63-1; (hydrocortisone) 50-23-7; (genistein) 446-72-0

CHEMICAL NAME: Drug Trade Name: ro 24 5531

L88 ANSWER 38 OF 49 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 3

ACCESSION NUMBER: 2005:115743 BIOSIS
DOCUMENT NUMBER: PREV200500114996
TITLE: Induction of **ovarian** cancer cell **apoptosis** by 1,25-**dihydroxyvitamin D3** through the down-regulation of telomerase.
AUTHOR(S): Jiang, Feng; Bao, Junying; Li, Pengfei; Nicosia, Santo V.; Bai, Wenlong [Reprint Author]
CORPORATE SOURCE: Coll MedDept Pathol, Univ S Florida, 12901 Bruce B Downs Blvd,MDC 11, Tampa, FL, 33612, USA
wbai@hsc.usf.edu
SOURCE: Journal of Biological Chemistry, (December 17 2004) Vol. 279, No. 51, pp. 53213-53221. print.
CODEN: JBCHA3. ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 23 Mar 2005
Last Updated on STN: 23 Mar 2005

ABSTRACT:The maintenance of telomere length is required for continued cell proliferation, and apprx85-90% of human cancers, including **ovarian** ***epithelial*** cancers (OCa), show high activity of telomerase. In the present study we report that 1,25-**dihydroxyvitamin D3** (1,25(OH)2VD3) induces OCa cell **apoptosis** by down-regulating telomerase. Quantitative reverse transcription-PCR analysis shows that 1,25(OH)2VD3 decreases the level of human telomerase reverse transcriptase (hTERT) mRNA, the catalytic subunit of telomerase. The decrease is not due to transcriptional repression through the putative **vitamin D** response element present in the 5' regulatory region of hTERT gene. Instead,

1,25(OH)2VD3 decreases the stability of the hTERT mRNA. Stable expression of hTERT in OCa cells decreases their response to 1,25(OH)2VD3-induced growth suppression. Although the cell cycle progression of these clones stably expressing hTERT is inhibited by 1,25(OH)2VD3 to a similar degree as that of the parental cells, these clones are more resistant to **apoptosis** induced by 1,25(OH)2VD3. In contrast to parental cells, which lose proliferation potential after the 1,25(OH)2VD3 treatment, hTERT-expressing clones resume rapid growth after withdrawal of 1,25(OH)2VD3. Overall, the study suggests that the down-regulation of telomerase activity by 1,25(OH)2VD3 and the resulting **cell death** are important components of the response of OCa cells to 1,25(OH)2VD3-induced growth suppression.

CONCEPT CODE: Enzymes - General and comparative studies: coenzymes 10802
Reproductive system - Physiology and biochemistry 16504
Neoplasms - Pathology, clinical aspects and systemic effects 24004

INDEX TERMS: Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); Reproductive System (Reproduction); Tumor Biology

INDEX TERMS: Chemicals & Biochemicals
1,25-**dihydroxyvitamin D3**; telomerase: down-regulation; telomerase reverse transcriptase mRNA: telomerase catalytic subunit

INDEX TERMS: Methods & Equipment
quantitative reverse transcriptase-polymerase chain reaction: genetic techniques, laboratory techniques

ORGANISM: Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
OCa cell line (cell line): **ovarian epithelial** cancer cell line
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

REGISTRY NUMBER: **32222-06-3Q** (1,25-**dihydroxyvitamin D3**)
32511-63-0Q (1,25-**dihydroxyvitamin D3**)
120178-12-3 (telomerase)

L88 ANSWER 39 OF 49 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 6

ACCESSION NUMBER: 2004:417640 BIOSIS
DOCUMENT NUMBER: PREV200400418544
TITLE: Increased **apoptosis** of periprostatic adipose tissue in VDR null mice.
AUTHOR(S): Guzey, Meral; Jukic, Drazen; Arlotti, Julie; Acquafondata, Marie; Dhir, Rajiv; Getzenberg, Robert H. [Reprint Author]
CORPORATE SOURCE: Shadyside Med Ctr, 5200 Ctr Ave,Suite G42, Pittsburgh, PA, 15232, USA
getzenbergrh@upmc.edu
SOURCE: Journal of Cellular Biochemistry, (September 1 2004) Vol. 93, No. 1, pp. 133-141. print.
ISSN: 0730-2312 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 27 Oct 2004
Last Updated on STN: 27 Oct 2004

Searched by Barb O'Bryen, STIC 2-2518

ABSTRACT:The **vitamin D** receptor (VDR) is a member of the steroid/retinoid receptor superfamily of nuclear receptors that controls mineral ion homeostatis and has potential tumor-suppressive functions for various cancer types, specifically prostate cancer. A VDR ablated transgenic animal model (VDDRII, **vitamin D**-dependent rickets type II) has been developed and the animals typically have various diseases including, hypocalcemia, hyperparathyroidism, rickets, osteomalacia, and alopecia. This transgenic mouse system provides us with a model to decipher the influences of the VDR on prostatic growth and function. VDRs are abundant both in prostatic ***epithelial*** and stromal cells, and **vitamin D** signaling can be studied in this model. Although, there were no gross differences between the prostate tissue of the experimental and control groups, VDR null mice showed fat necrosis and individual cell **apoptosis** in the periprostatic adipose tissue. This indicates a possible role of VDR in the signaling pathways resulting the prostate. This may be particularly attractive for VDR targets for the inhibition of cancer progression using VD3 and its analogs as potential **chemo-preventive** agents. Copyright 2004 Wiley-Liss, Inc.

CONCEPT CODE:
Cytology - General 02502
Cytology - Animal 02506
Biochemistry studies - General 10060
Biochemistry studies - Vitamins 10063
Biochemistry studies - Proteins, peptides and amino acids 10064
Pathology - General 12502
Pathology - Therapy 12512
Urinary system - Pathology 15506
Reproductive system - Physiology and biochemistry 16504
Reproductive system - Pathology 16506
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008

INDEX TERMS:
Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Reproductive System (Reproduction); Tumor Biology

INDEX TERMS:
Parts, Structures, & Systems of Organisms
epithelial cells: reproductive system; periprostatic adipose tissue, **apoptosis**; prostate: reproductive system, function, growth; stromal cells: reproductive system

INDEX TERMS:
Diseases
prostate cancer: neoplastic disease, reproductive system disease/male, urologic disease, drug therapy, pathology, prevention and control
Prostatic Neoplasms (MeSH)

INDEX TERMS:
Chemicals & Biochemicals
vitamin D receptor [VDR]: role; **vitamin D**-3: antineoplastic-drug, vitamin-drug

INDEX TERMS:
Miscellaneous Descriptors
cancer progression inhibition; fat necrosis; individual cell **apoptosis**; **vitamin D** signaling

ORGANISM:
Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse (common): transgenic
Taxa Notes

Searched by Barb O'Bryen, STIC 2-2518

Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
REGISTRY NUMBER: 67-97-0 (**vitamin D**-3)

L88 ANSWER 40 OF 49 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 7
ACCESSION NUMBER: 2003:499424 BIOSIS
DOCUMENT NUMBER: PREV200300501421
TITLE: Pathways mediating the growth-inhibitory actions of **vitamin D** in prostate cancer.
AUTHOR(S): Peehl, Donna M.; Krishnan, Aruna V.; Feldman, David [Reprint Author]
CORPORATE SOURCE: Department of Medicine, Stanford University School of Medicine, Stanford, CA, 94305, USA feldman@cmgm.stanford.edu
SOURCE: Journal of Nutrition, (July 2003) Vol. 133, No. 7S Supplement, pp. 2461S-2469S. print. ISSN: 0022-3166 (ISSN print).
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 29 Oct 2003
Last Updated on STN: 29 Oct 2003
ABSTRACT:**Vitamin D** is emerging as an important dietary factor that affects the incidence and progression of many malignancies including prostate cancer. The active form of **vitamin D**, 1,25-dihydroxycholecalciferol (1,25(OH)2D3), inhibits the growth and stimulates the differentiation of prostate cancer cells. We have studied primary cultures of normal and cancer-derived prostatic **epithelial** cells as well as established human prostate cancer cell lines to elucidate the molecular pathways of 1,25(OH)2D3 actions. These pathways are varied and appear to be cell specific. In LNCaP cells, 1,25(OH)2D3 mainly causes growth arrest through the induction of insulin-like growth factor binding protein-3 and also stimulates **apoptosis** to a much smaller extent. We have used cDNA-microarray analyses to identify additional genes that are regulated by 1,25(OH)2D3 and to raise novel therapeutic targets for use in the ***chemoprevention*** or treatment of prostate cancer. Less calcemic analogs of 1,25(OH)2D3 that have more antiproliferative activity are being developed that will be more useful clinically. In target cells, 1,25(OH)2D3 induces 24-hydroxylase, the enzyme that catalyzes its self inactivation. Cotreatment with 24-hydroxylase inhibitors enhances the antiproliferative activity of 1,25(OH)2D3. The combination of other anticancer agents such as retinoids with ***vitamin*** **D** offers another promising therapeutic approach. A small clinical trial has shown that 1,25(OH)2D3 can slow the rate of prostate-specific antigen increase in prostate cancer patients, which demonstrates proof of the concept that **vitamin D** or its analogs are clinically effective. Our research is directed at understanding the mechanisms of **vitamin D** action in prostate cells with the goal of developing **chemoprevention** and treatment strategies to improve prostate cancer therapy.
CONCEPT CODE: Cytology - General 02502
Cytology - Animal 02506
Cytology - Human 02508
Genetics - General 03502
Genetics - Human 03508
Biochemistry studies - Vitamins 10063
Biochemistry studies - Proteins, peptides and amino acids 10064
Biochemistry studies - Lipids 10066
Biochemistry studies - Sterols and steroids 10067

Pathology - Therapy 12512
Urinary system - Pathology 15506
Reproductive system - Physiology and biochemistry 16504
Reproductive system - Pathology 16506
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008

INDEX TERMS: Major Concepts
Cell Biology; Molecular Genetics (Biochemistry and Molecular Biophysics); Oncology (Human Medicine, Medical Sciences); Pharmacology; Urology (Human Medicine, Medical Sciences)

INDEX TERMS: Parts, Structures, & Systems of Organisms
prostatic **epithelial** cells: reproductive system

INDEX TERMS: Diseases
prostate cancer: neoplastic disease, reproductive system disease/male, urologic disease, drug therapy, prevention and control, therapy
Prostatic Neoplasms (MeSH)

INDEX TERMS: Chemicals & Biochemicals
1,25-dihydroxycholecalciferol [1,25(OH)-2-D-3]: antineoplastic-drug; 24-hydroxylase; 24-hydroxylase inhibitors: antineoplastic-drug, enzyme inhibitor-drug; insulin-like growth factor binding protein-3; prostate-specific antigen [EC 3.4.21.77]; retinoids: antineoplastic-drug; **vitamin D**: antineoplastic-drug, growth-inhibitory actions; **vitamin D** analogs: antineoplastic-drug

INDEX TERMS: Methods & Equipment
cDNA-microarray analysis [complementary DNA-microarray analysis]: genetic techniques, laboratory techniques; **chemoprevention**: clinical techniques, therapeutic and prophylactic techniques

INDEX TERMS: Miscellaneous Descriptors
apoptosis; cell differentiation; growth arrest

ORGANISM: Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
LNCaP cell line (cell line): human prostate cancer cells
human (common): patient
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

REGISTRY NUMBER: **32222-06-3Q** (1,25-dihydroxycholecalciferol)
32511-63-0Q (1,25-dihydroxycholecalciferol)
32222-06-3Q (1,25(OH)-2-D-3)
32511-63-0Q (1,25(OH)-2-D-3)
1406-16-2 (**vitamin D**)

L88 ANSWER 41 OF 49 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 8

ACCESSION NUMBER: 2003:499418 BIOSIS
DOCUMENT NUMBER: PREV200300501415
TITLE: **Vitamin D**-3 receptor as a target for breast cancer prevention.

AUTHOR(S): Welsh, JoEllen [Reprint Author]; Wietzke, Jennifer A.; Zinser, Glendon M.; Byrne, Belinda; Smith, Kelly; Narvaez, Carmen J.
CORPORATE SOURCE: Department of Biological Sciences, University of Notre Dame, Notre Dame, IN, 46556, USA
jwelsh3@nd.edu
SOURCE: Journal of Nutrition, (July 2003) Vol. 133, No. 7S Supplement, pp. 2425S-2433S. print.
ISSN: 0022-3166 (ISSN print).
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 29 Oct 2003
Last Updated on STN: 29 Oct 2003
ABSTRACT:The **vitamin D**-3 receptor (VDR) is a nuclear receptor that modulates gene expression when complexed with its ligand 1-alpha,25-dihydroxycholecalciferol (1,25(OH)2-D3), which is the biologically active form of **vitamin D**-3. The cellular effects of VDR signaling include growth arrest, differentiation and/or induction of ***apoptosis*** , which indicate that the **vitamin D** pathway participates in negative-growth regulation. Although much attention has been directed in recent years toward the development of synthetic ***vitamin*** **D** analogs as therapeutic agents for a variety of human cancers including those derived from the mammary gland, studies on ***vitamin*** **D** as a **chemopreventive** agent for breast cancer have been quite limited. The VDR is expressed in normal mammary gland, where it functions to oppose estrogen-driven proliferation and maintain differentiation; this suggests that 1,25(OH)2-D3 participates in negative-growth regulation of mammary **epithelial** cells. Furthermore, preclinical studies show that **vitamin D** compounds can reduce breast cancer development in animals, and human data indicate that both ***vitamin*** **D** status and genetic variations in the VDR may affect breast cancer risk. Collectively, findings from cellular, molecular and population studies suggest that the VDR is a nutritionally modulated growth-regulatory gene that may represent a molecular target for ***chemoprevention*** of breast cancer.
CONCEPT CODE:
Cytology - General 02502
Cytology - Animal 02506
Cytology - Human 02508
Genetics - General 03502
Genetics - Human 03508
Biochemistry studies - Vitamins 10063
Pathology - Therapy 12512
Reproductive system - Physiology and biochemistry 16504
Reproductive system - Pathology 16506
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008
INDEX TERMS: Major Concepts
Cell Biology; Molecular Genetics (Biochemistry and Molecular Biophysics); Pharmacology; Reproductive System (Reproduction); Tumor Biology
INDEX TERMS: Parts, Structures, & Systems of Organisms
mammary **epithelial** cells: reproductive system; mammary gland: reproductive system
INDEX TERMS: Diseases
breast cancer: neoplastic disease, reproductive system disease/female, prevention and control

Searched by Barb O'Bryen, STIC 2-2518

Breast Neoplasms (MeSH)
INDEX TERMS: Chemicals & Biochemicals
1-alpha,25-dihydroxycholecalciferol [1,25(OH)-2-D-3]; estrogen; synthetic **vitamin D** analogs: antineoplastic-drug; **vitamin D**-3: antineoplastic-drug, **chemopreventive** agent; **vitamin D**-3 receptor [VDR]
INDEX TERMS: Miscellaneous Descriptors
apoptosis; cell differentiation; cell proliferation; gene expression; growth arrest; negative-growth regulation
ORGANISM: Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human (common)
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
REGISTRY NUMBER: **32222-06-3** (1-alpha,25-dihydroxycholecalciferol)
32222-06-3 (1,25(OH)-2-D-3)
67-97-0 (**vitamin D**-3)
GENE NAME: human VDR gene [human **vitamin D**-3 receptor gene] (Hominidae): nutritionally modulated growth-regulatory gene

L88 ANSWER 42 OF 49 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:556956 BIOSIS
DOCUMENT NUMBER: PREV200200556956
TITLE: Prevention of **ovarian** cancer by administration of a **vitamin D** compound.
AUTHOR(S): Rodriguez, Gustavo C. [Inventor]; Whitaker, Regina Salas [Inventor]
CORPORATE SOURCE: ASSIGNEE: New Life Pharmaceuticals Inc.
PATENT INFORMATION: US 6444658 September 03, 2002
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Sep. 3, 2002) Vol. 1262, No. 1. http://www.uspto.gov/web/menu/patdata.html. e-file. CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 30 Oct 2002
Last Updated on STN: 30 Oct 2002
ABSTRACT:The present invention relates to methods for preventing the development of **epithelial ovarian** cancer by administering a ***Vitamin*** **D** compound in an amount capable of increasing ***apoptosis*** in non-neoplastic **ovarian epithelial** cells of the female subject.
NAT. PATENT. CLASSIF.:514167000
CONCEPT CODE: Reproductive system - Pathology 16506
Pathology - Therapy 12512
Pharmacology - General 22002
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008
INDEX TERMS: Major Concepts
Pharmacology

Searched by Barb O'Bryen, STIC 2-2518

INDEX TERMS: Diseases
ovarian cancer: neoplastic disease, reproductive system disease/female, drug therapy
Ovarian Neoplasms (MeSH)
INDEX TERMS: Chemicals & Biochemicals
vitamin D compound: antineoplastic-drug

L88 ANSWER 43 OF 49 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:402060 BIOSIS
DOCUMENT NUMBER: PREV200200402060
TITLE: Prevention of **ovarian** cancer by administration of a **vitamin D** compound.
AUTHOR(S): Rodriguez, Gustavo C. [Inventor, Reprint author]; Whitaker, Regina Salas [Inventor]
CORPORATE SOURCE: Durham, NC, USA
ASSIGNEE: New Life Pharmaceuticals Inc.
PATENT INFORMATION: US 6407082 June 18, 2002
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (June 18, 2002) Vol. 1259, No. 3. http://www.uspto.gov/web/menu/patdata.html. e-file. CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Jul 2002
Last Updated on STN: 24 Jul 2002
ABSTRACT:The present invention relates to methods for preventing the development of **epithelial ovarian** cancer by administering a ***Vitamin*** **D** compound in an amount capable of increasing ***apoptosis*** in non-neoplastic **ovarian epithelial** cells of the female subject.
NAT. PATENT. CLASSIF.:514167000
CONCEPT CODE: Reproductive system - Pathology 16506
Pathology - Therapy 12512
Pharmacology - General 22002
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008
INDEX TERMS: Major Concepts
Gynecology (Human Medicine, Medical Sciences); Oncology (Human Medicine, Medical Sciences); Pharmacology
INDEX TERMS: Diseases
ovarian cancer: neoplastic disease, reproductive system disease/female
Ovarian Neoplasms (MeSH)
INDEX TERMS: Chemicals & Biochemicals
vitamin D compound: antineoplastic-drug

L88 ANSWER 44 OF 49 DISSABS COPYRIGHT (C) 2005 ProQuest Information and Learning Company; All Rights Reserved on STN
ACCESSION NUMBER: 2003:56475 DISSABS Order Number: AAI3082972
TITLE: **Vitamin D** and genistein inhibit growth of human prostatic **epithelial** cells
AUTHOR: Rao, Anuradha [Ph.D.]; Cramer, Scott D. [advisor]
CORPORATE SOURCE: Wake Forest University (0248)
SOURCE: Dissertation Abstracts International, (2003) Vol. 64, No. 3B, p. 1101. Order No.: AAI3082972. 210 pages.
DOCUMENT TYPE: Dissertation

FILE SEGMENT: DAI
LANGUAGE: English
ENTRY DATE: Entered STN: 20031201
Last Updated on STN: 20031201

ABSTRACT:

Prostate cancer is a significant problem in the Western world. However, the incidence and death due to this disease is less common in China and Japan where diets are rich in **vitamin D** and soy. Extensive epidemiological and laboratory data provide evidence for the growth inhibitory actions of **vitamin D** and genistein, a soy isoflavone. Here, we conducted experiments to determine the actions of these compounds when used alone and in combination, on prostate cancer cell lines as well as on primary human prostatic **epithelial** cells (HPECs) derived from benign and cancer prostate tissue.

The enzyme, 25-**hydroxyvitamin D** 1alpha-hydroxylase (1αOHase), converts the non-calcemic prohormone, 25-**hydroxyvitamin D3** [25OHD3] to 1,25 **dihydroxyvitamin D3** [1,25(OH)2D 3], the hormonally active form of **vitamin D.** We demonstrated the presence of this enzyme in benign and cancer prostate tissue as well as in HPECs derived from these tissues. Both benign and cancer tissue derived HPECs are growth inhibited by 25OHD3 and 1,25(OH)2D3. Treatment of HPECs and LNCaP cells with both forms of **vitamin D** causes a G0/1 cell cycle arrest. The presence of 1αOHase, and that cancer derived HPECs are growth inhibited by 25OHD3 makes this non calcemic compound potentially useful in prostate cancer **chemoprevention.**

Subsequently, we determined that genistein is also a potent growth inhibitor of benign and cancer derived HPECs. Additionally, HPECs are more sensitive to growth inhibition by genistein than are prostate cancer cell lines such as LNCaP and PC-3. Genistein inhibits growth of HPECs by causing a G 2M arrest, while in LNCaP cells genistein causes a G0/1 arrest. When used in combination, genistein synergizes with 1,25(OH)2D 3 to inhibit growth of HPECs and LNCaP cells. Genistein also synergizes with 25OHD3 to inhibit growth of HPECs. At doses used in our experiments neither genistein nor **vitamin D** metabolites caused **apoptosis.**

We then examined the molecular actions of these compounds. In combination, 1,25(OH)2D3 and genistein caused a cooperative increase in protein levels of the cyclin dependent kinase inhibitor p21 in LNCaP cells. Subsequently, the expression of p21 was "knocked-down" in LNCaP cells using siRNA. When these cells were treated with 1,25(OH)2D 3 and genistein both alone and in combination, growth inhibition was not significantly different from that of untreated cells. Therefore, the ability of these compounds to inhibit growth is dependent on the presence of p21. Additionally, in combination, 1,25(OH)2D3 and genistein caused a cooperative increase in protein levels of the **vitamin D** receptor (VDR), from 4 until 96 hours after treatment.

We conclude that 1,25(OH)2D3 and genistein by cooperatively upregulating both p21 and VDR cause a synergistic growth inhibition of prostate cancer cells,

potentially by enhancing the growth inhibitory actions of 1,25(OH) 2D3. Therefore, these compounds could be used in prostate cancer **chemoprevention** or as adjuvants in prostate cancer therapy.

CLASSIFICATION: 0307 BIOLOGY, MOLECULAR; 0992 HEALTH SCIENCES, ONCOLOGY

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ACCESSION NUMBER: 2004:70304 DISSABS Order Number: AAI3131262

TITLE: **Chemopreventive** function of retinoid X receptors in human squamous cell carcinoma of the skin

AUTHOR: Li, Guojun [Ph.D.]; Clifford, John L. [advisor]

CORPORATE SOURCE: The University of Texas Health Sciences Center at Houston School of Public Health (0219)

SOURCE: Dissertation Abstracts International, (2002) Vol. 65, No. 4B, p. 1811. Order No.: AAI3131262. 140 pages.

DOCUMENT TYPE: Dissertation

FILE SEGMENT: DAI

LANGUAGE: English

ENTRY DATE: Entered STN: 20041217
Last Updated on STN: 20041217

ABSTRACT:

Retinoid therapy has been successful for the treatment of skin squamous cell carcinoma (SCC). A suppression of the predominant retinoid X receptor expressed in skin, retinoid X receptor α (RXRα), has been reported in skin SCC. These observations have led to the hypothesis that retinoid receptor loss contributes to the tumorigenic phenotype of **epithelial** cancers. To test this hypothesis, the RXRα gene was mapped in order to generate a targeting construct. Additionally the transcriptional regulation of the human RXRα a gene in keratinocytes was characterized after identifying the transcription initiation sites, the promoter, and enhancer regions of this gene. The structure is highly conserved between human and mouse. A nontumorigenic human skin-derived cell line called near diploid immortalized keratinocytes (NIKS) has the advantage of growing as organotypic raft cultures, under physiological conditions closely resembling in-vivo squamous stratification. We have exploited the raft culture technique to develop an in-vitro model for skin SCC progression that includes the NIKS cells, HaCaT cells, a premalignant cell line, and SRB 12-p9 cells, a tumorigenic SCC skin cell line. The differentiation, proliferation and nuclear receptor ligand response characteristics of this system were studied and significant and novel results were obtained. RXRs are obligate heterodimerization partners with many of the nuclear hormone receptors, including retinoic acid receptors (RARs), **vitamin D3** receptors (VDR), thyroid hormone receptors (T3 R) and peroxisome proliferator activate receptors (PPARs), which are all known to be active in skin. Treatment of the three cell lines in raft culture with the RXR specific ligand BMS649, BMS961 (RARγ-specific), **vitamin D3** (VDR ligand), thryoid hormone (T3R ligand) and clofibrate (PPARa ligand), and the combination of BMS649 with each of the 4 receptor partner ligands, resulted in distinct effects on differentiation, proliferation and **apoptosis.** The effects of activation of RXRs in each of the four-receptor pathways; in the context of skin

SCC progression, with an emphasis on the VDR/RXR pathway, are discussed. These studies will lead to a better understanding of RXRα action in human skin and will help determine its role in SCC tumorigenesis, as well as its potential as a target for the prevention, treatment, and control of skin cancer.

CLASSIFICATION: 0573 HEALTH SCIENCES, PUBLIC HEALTH; 0307 BIOLOGY, MOLECULAR; 0992 HEALTH SCIENCES, ONCOLOGY

L88 ANSWER 46 OF 49 TOXCENTER COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:237466 TOXCENTER
COPYRIGHT: Copyright 2005 ACS
DOCUMENT NUMBER: CA14003023367Y
TITLE: Efficacy and mechanism of action of 1α-hydroxy-24-ethyl-**cholecalciferol** (1α[OH]D5) in breast cancer prevention and therapy
AUTHOR(S): Hussain, Erum A.; Mehta, Rajeshwari R.; Ray, Rahul; Das Gupta, Tapas K.; Mehta, Rajendra G.
CORPORATE SOURCE: Department of Surgical Oncology, University of Illinois at Chicago, Chicago, IL, 60612, USA.
SOURCE: Recent Results in Cancer Research, (2003) Vol. 164, No. Vitamin D Analogs in Cancer Prevention and Therapy, pp. 393-411.
CODEN: RRCRBU. ISSN: 0080-0015.
COUNTRY: UNITED STATES
DOCUMENT TYPE: Journal
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 2003:748392
LANGUAGE: English
ENTRY DATE: Entered STN: 20030930
Last Updated on STN: 20040113

ABSTRACT:
A review. It is now well established that the active metabolite of ***vitamin*** **D3**, 1α,25(OH)2D3, regulates cell growth and differentiation in various in vitro cancer models. However, its clin. use is precluded due to its hypercalcemic activity in vivo. Hence, several less calcemic **vitamin D** analogs have been synthesized and evaluated for their **chemopreventive** and therapeutic efficacy in exptl. carcinogenesis models. A novel analog of **vitamin D3**, 1α-hydroxy-24-ethyl- **cholecalciferol** (1α[OH]D5), has currently been under investigation in the authors' laboratory for its application in breast cancer prevention and therapy. 1α(OH)D5 had been shown to inhibit development of estrogen- and progesterone-dependent ductal lesions as well as steroid hormone-independent alveolar lesions in a mammary gland organ culture (MMOC) model. Moreover, the inhibitory effect was more significant if 1α(OH)D5 was present during the promotional phase of the lesion development. The growth inhibitory effect of 1α(OH)D5 has also been manifested in several breast cancer cell lines, including BT-474 and MCF-7. Breast cancer cell lines that responded to 1α(OH)D5 treatment were ***vitamin*** **D** receptor pos. (VDR+). **Vitamin D** receptor-neg. (VDR-) cell lines, such as MDA-MB-231 and MDA-MB-435, did not show growth inhibition upon incubation with 1α(OH)D5. This suggests the requirement of VDR in 1α(OH)D5-mediated growth effects. Interestingly, breast cancer cells that were VDR+ as well as estrogen receptor pos. (ER+) showed cell cycle arrest and **apoptosis**, while VDR+ but ER- cells (UISO-BCA-4 breast cancer cells) showed enhanced expression of various differentiation markers with 1α(OH)D5 treatment. Transcription and expression of estrogen-inducible genes, progesterone receptor (PR) and trefoil factor 1 (pS2), were significantly down-regulated in ER+ BT-474 cells with 1α(OH)D5 treatment. This implies a differential effect of 1α(OH)D5

on ER+ vs. ER- cells. Addnl., comparison between the effects of 1α(OH)D5 on normal vs. transformed cells indicated that 1α(OH)D5 does not suppress cell proliferation of normal **epithelial** cells but selectively targets growth of transformed cells. The authors extended their expts. to determine in vivo effects of 1α(OH)D5 using an MNU-induced mammary carcinogenesis model in female Sprague-Dawley rats. Results showed that 1α(OH)D5 (25-50 μg/kg diet) decreased the incidence and multiplicity of mammary tumors in these rats. In addition, it increased the latency period of early precancerous lesions. Similar studies, with DMBA as a carcinogen in younger rats, showed that 1α(OH)D5 supplementation was effective in reducing onset of carcinogenesis in rats and the effect was largely reflected during the promotional phase of carcinogenesis. Recently, a preclin. toxicity profile for 1α(OH)D5 was completed in rats and dogs that provides estimation of the maximum tolerated dose in mammals. Based on their findings, the authors will shortly be initiating a 1α(OH)D5 phase I clin. trial for breast cancer patients.

CLASSIFICATION CODE: 2-0
SUPPLEMENTARY TERMS: Miscellaneous Descriptors
review **cholecalciferol** analog breast cancer prevention therapy; hydroxyethylcholecalciferol breast cancer prevention therapy review
REGISTRY NUMBER: 7440-70-2 (Calcium)
57-83-0 (Progesterone)
187935-17-7 (1α-Hydroxyvitamin D5)

L88 ANSWER 47 OF 49 TOXCENTER COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:237462 TOXCENTER
COPYRIGHT: Copyright 2005 ACS
DOCUMENT NUMBER: CA14003023363U
TITLE: The role of **vitamin D** in prostate cancer
AUTHOR(S): Krishnan, Aruna V.; Peehl, Donna M.; Feldman, David
CORPORATE SOURCE: Department of Medicine, Division of Endocrinology, Stanford University School of Medicine, Stanford, CA, 94305-5103, USA.
SOURCE: Recent Results in Cancer Research, (2003) Vol. 164, No. Vitamin D Analogs in Cancer Prevention and Therapy, pp. 205-221.
CODEN: RRCRBU. ISSN: 0080-0015.
COUNTRY: UNITED STATES
DOCUMENT TYPE: Journal
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 2003:748378
LANGUAGE: English
ENTRY DATE: Entered STN: 20030930
Last Updated on STN: 20040113

ABSTRACT:
A review. Prostate cancer (PCa) cells harbor receptors for **vitamin** ***D*** (VDR) as well as androgens (AR). 1,25-**Dihydroxyvitamin** ***D3*** [1,25(OH)2D3] increases AR expression and enhances androgen actions linking the 2 receptor systems. 1,25(OH)2D3 exhibits antiproliferative activity in both AR-pos. and AR-neg. PCa cells. Less calcemic analogs of 1,25(OH)2D3, with more antiproliferative activity, are being developed and will be more useful clin. The mechanisms underlying differential analog activity are being investigated. In target cells, 1,25(OH)2D3 induces 24-hydroxylase, the enzyme that catalyzes its self-inactivation. Co-treatment with 24-hydroxylase inhibitors enhances the antiproliferative activity of ***calcitriol.*** Primary cultures of normal or cancer-derived prostatic ***epithelial*** cells express 1α-hydroxylase, the enzyme that catalyzes the synthesis of 1,25(OH)2D3, the levels being much lower in the

cancer-derived cells and in PCa cell lines. This finding raises the possibility of using 25-**hydroxyvitamin D3** [25(OH)D3] as a ***chemopreventive*** agent in PCa. In LNCaP human PCa cells, 1,25(OH)2D3 and its analogs exert antiproliferative activity predominantly by cell cycle arrest, but also induce **apoptosis**, although to a much lesser degree. Growth arrest is mediated by induction of IGF binding protein-3 (IGFBP-3), which in turn increases the expression of the cell cycle inhibitor p21, leading to growth arrest. Other actions of 1,25(OH)2D3 in PCa cells include promotion of pro-differentiation effects and inhibition of tumor cell invasion, metastasis and angiogenesis. Combination therapy with retinoids, other anticancer agents or 24-hydroxylase inhibitors augments the inhibitory activity of 1,25(OH)2D3 in PCa and provides another effective approach in PCa treatment. Small clin. trials have shown that 1,25(OH)2D3 can slow the rate of prostate specific antigen (PSA) rise in PCa patients, demonstrating proof of concept that 1,25(OH)2D3 or its analogs will be clin. effective in PCa therapy. Current research involves further investigation of the role of 1,25(OH)2D3 and its analogs for the therapy or **chemoprevention** of PCa.

CLASSIFICATION CODE: 2-0
SUPPLEMENTARY TERMS: Miscellaneous Descriptors
review **vitamin D** androgen receptor
antitumor prostate cancer; **dihydroxyvitamin D3** antitumor prostate cancer review
REGISTRY NUMBER: **32222-06-3** (1,25-**Dihydroxyvitamin D3**)

L88 ANSWER 48 OF 49 TOXCENTER COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:155064 TOXCENTER
COPYRIGHT: Copyright 2005 ACS
DOCUMENT NUMBER: CA12909108332F
TITLE: Vitamin E: mechanisms of action as tumor cell growth inhibitors
AUTHOR(S): Kline, Kimberly; Yu, Weiping; Sanders, Bob G.
CORPORATE SOURCE: Division of Nutrition, The University of Texas at Austin, Austin, TX, 78712, USA.
SOURCE: Cancer and Nutrition, (1998) pp. 37-53.
CODEN: 66HKAD.
COUNTRY: UNITED STATES
DOCUMENT TYPE: Conference
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 1998:401162
LANGUAGE: English
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20020521

ABSTRACT:
A review with 57 refs. Vitamin E and some of its derivs., notably the succinate ester of RRR-α-tocopherol, RRR-α-tocopheryl succinate (vitamin E succinate, VES), are being studied for potential use as anti-cancer agents. VES has been shown to inhibit the proliferation of several tumor cell types in vitro as well as in vivo. VES is noteworthy not only for its antiproliferative effects on tumor cells but also for its low toxicity toward normal cell types. Although the mechanisms of growth inhibition of tumor cells by VES are not yet fully understood, it is clear that VES possesses unique biol. properties independent of those of RRR-α-tocopherol (natural vitamin E) which is well known for its antioxidant properties. DNA synthesis arrest, induction of cellular differentiation, enhanced secretion and activation of potent **epithelial** cell growth inhibitors called transforming growth factor-betas (TGF-β), and enhanced expression of cell surface proteins required for TGF-β signalling, as well as induction of programmed **cell death** (**apoptosis**) have been observed in VES-treated tumor cells. These interesting biol. properties place VES among

a select group of compds. that are being tested for both ***chemopreventive*** as well as chemotherapeutic actions; namely, monoterpenes (d-limonene and perillyl alc.), retinoids, and **vitamin** ***D*** analogs.
CLASSIFICATION CODE: 18-0
SUPPLEMENTARY TERMS: Miscellaneous Descriptors
review tocopherol mechanism antitumor agent
REGISTRY NUMBER: 1406-18-4 (Vitamin E)
4345-03-3 (α-Tocopheryl succinate)

L88 ANSWER 49 OF 49 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-068898 [07] WPIDS
CROSS REFERENCE: 1998-207141 [18]; 1999-060022 [05]; 2002-096564 [13]; 2002-105573 [14]; 2003-352322 [33]; 2004-431421 [40]; 2004-652057 [63]
DOC. NO. CPI: C2004-028427
TITLE: Formulating a regimen for the prevention of **epithelial ovarian** cancer, comprises selection of an agent which upregulates transforming growth factor-beta expression in the **ovarian epithelium.**
DERWENT CLASS: B01
INVENTOR(S): RODRIGUEZ, G C
PATENT ASSIGNEE(S): (RODR-I) RODRIGUEZ G C; (RODR-I) RODRIGUEZ G
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 2003125229	A1	20030703	(200407)*		30	A61K031-00
US 6765002	B2	20040720	(200448)			A61K031-56

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2003125229	A1	US 2000-528963	20000321
US 6765002	B2	US 2000-528963	20000321

PRIORITY APPLN. INFO: US 2000-528963 20000321
INT. PATENT CLASSIF.:
MAIN: A61K031-00; A61K031-56
SECONDARY: A61K031-59
BASIC ABSTRACT:
US2003125229 A UPAB: 20041001
NOVELTY - Formulating a regimen for the prevention of **epithelial ovarian** cancer, comprises selecting an agent (I) which can upregulate transforming growth factor- beta (TGF- beta) expression in the **ovarian epithelium.**
ACTIVITY - Cytostatic.
MECHANISM OF ACTION - **Ovarian epithelial** cells transforming growth factor- beta (TGF- beta) expression promoter; **Ovarian epithelial** cells **apoptosis** promoter.
A cell line M-100, a spontaneously immortalized normal human **ovarian epithelial** cell culture, was plated in 24 well plates at a concentration of 100000 cells per well. After 24 hours the wells were treated with either levonorgestrel (20 ng/ml) or control medium and incubated. After 96 hours, the cell lysates were extracted from each well, normalized for cell number and analyzed for DNA-histone complexes

indicative of **apoptosis**. A statistically significant (100%) increase in **apoptosis** was measured in M-100 cells treated with levonorgestrel as compared to controls (p less than 0.05).

USE - The composition is useful for the prevention of **epithelial ovarian** cancer (claimed).

ADVANTAGE - The TGF- beta expression provides protection against the development of **epithelial ovarian** cancer by inhibition of proliferation of **ovarian epithelial** cells, induction of differentiation of **ovarian epithelial** cells, activation of enhancement of the protective effects of the other agents such as **vitamin D** and/or **apoptosis** of **ovarian epithelial** cells.

Dwg.0/0

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B01-A01; B01-C03; B01-C05; B14-H01; B14-L01

FILE 'HOME' ENTERED AT 12:56:16 ON 10 MAY 2005

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=> d his full

     (FILE 'HOME' ENTERED AT 11:58:22 ON 10 MAY 2005)

     FILE 'REGISTRY' ENTERED AT 11:59:23 ON 10 MAY 2005
                E VITAMIN D/CN
L1            1 SEA ABB=ON  "VITAMIN D"/CN
                E 25-HYDROXYVITAMIN D/CN
                E 25-HYDROXYVITAMIN D3/CN
L2            1 SEA ABB=ON  "25-HYDROXYVITAMIN D3"/CN
                E 1,25-DIHYDROXYVI/CN
L3            2 SEA ABB=ON  "1,25-DIHYDROXYVITAMIN D3"/CN
                E 1,25-DIHYDROXYCHOLECAL/CN
L4            2 SEA ABB=ON  "1,25-DIHYDROXYCHOLECALCIFEROL"/CN
L5            4 SEA ABB=ON  (L1 OR L2 OR L3 OR L4)

     FILE 'REGISTRY' ENTERED AT 12:01:36 ON 10 MAY 2005
                D IDE 1-4

     FILE 'CAPLUS' ENTERED AT 12:02:48 ON 10 MAY 2005
                SET LINE 250
                SET DETAIL OFF
                E US2003-781173/AP,PRN 25
                SET LINE LOGIN
                SET DETAIL LOGIN
L6         1379 SEA ABB=ON  RODRIGUEZ G?/AU
L7        22302 SEA ABB=ON  L5
L8            5 SEA ABB=ON  L6 AND L7
                D SCAN TI
L9        84060 SEA ABB=ON  OVAR?/OBI
L10           4 SEA ABB=ON  L8 AND L9
                D SCAN
                E APOPTOSIS+ALL/CT
L11       73956 SEA ABB=ON  APOPTOSIS/CT
                E EPITHELIUM+ALL/CT
L12       21981 SEA ABB=ON  EPITHELIUM/CT
L13        4865 SEA ABB=ON  L7(L)(BAC OR PAC OR PKT OR DMA OR THU)/RL
L14           4 SEA ABB=ON  L13 AND L11 AND L12
L15           1 SEA ABB=ON  L10 AND L14
                SAVE TEMP L14 COO173CA/A

     FILE 'CANCERLIT, MEDLINE' ENTERED AT 12:06:38 ON 10 MAY 2005
L16       29987 SEA ABB=ON  VITAMIN D+NT/CT
L17      103421 SEA ABB=ON  APOPTOSIS+NT/CT
L18      185782 SEA ABB=ON  EPITHELIAL CELLS+NT/CT
L19          22 SEA ABB=ON  L16 AND L17 AND L18
L20          17 DUP REM L19 (5 DUPLICATES REMOVED)
                     ANSWERS '1-5' FROM FILE CANCERLIT
                     ANSWERS '6-17' FROM FILE MEDLINE
                D TRIAL 1-5

     FILE 'MEDLINE' ENTERED AT 12:08:20 ON 10 MAY 2005
                E EPITHELIAL CELLS+NT/CT
                E VITAMIN D+NT/CT
                E APOPTOSIS+NT/CT
L21       15288 SEA ABB=ON  L16(L)(PD OR AD OR TU OR PK)/CT
L22          15 SEA ABB=ON  L21 AND L17 AND L18
                SAVE TEMP L22 COO173CANMED/A

     FILE 'EMBASE' ENTERED AT 12:10:08 ON 10 MAY 2005
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                E VITAMIN D+ALL/CT
L23        34864 SEA ABB=ON  VITAMIN D+NT/CT
                E APOPTOSIS+ALL/CT
L24        81091 SEA ABB=ON  APOPTOSIS/CT
                E EPITHELIAL CELL+ALL/CT
                E E2+ALL
L25       139809 SEA ABB=ON  EPITHELIUM CELL+NT/CT
                E OVARY/CT
                E E3+ALL
L26        49175 SEA ABB=ON  OVARY+NT/CT
L27           44 SEA ABB=ON  L23 AND L24 AND L25
L28        11662 SEA ABB=ON  L23(L)(PD OR PK OR AD OR DO OR DT)/CT
L29           26 SEA ABB=ON  L28 AND L24 AND L25
L30            1 SEA ABB=ON  L28 AND L24 AND L25 AND L26
L31            1 SEA ABB=ON  L28 AND L24 AND L26
                D TRIAL
                D TRIAL L30
                E EPITHELIUM+ALL/CT
L32       133976 SEA ABB=ON  EPITHELIUM+NT/CT
L33           16 SEA ABB=ON  L28/MAJ AND L24 AND (L25 OR L32)
                D TRIAL 1-8
L34      1280287 SEA ABB=ON  NEOPLASM+NT/CT
L35            7 SEA ABB=ON  L33 NOT L34
                D TRIAL 1-7
L36        91141 SEA ABB=ON  CELL PROLIFERATION/CT
L37            9 SEA ABB=ON  L33 AND L36
L38            6 SEA ABB=ON  L37 NOT L35
                D TRIAL 1-6
L39         7163 SEA ABB=ON  CHEMOPROPHYLAXIS/CT
L40       142668 SEA ABB=ON  DRUG EFFECT/CT
L41        16368 SEA ABB=ON  CANCER INHIBITION/CT
L42            6 SEA ABB=ON  L33 AND (L39 OR L40 OR L41)

     FILE 'CAPLUS' ENTERED AT 12:22:16 ON 10 MAY 2005
L43           10 SEA ABB=ON  L9 AND L11 AND L13
L44            9 SEA ABB=ON  L43 NOT L14
                D SCAN TI
L45            4 SEA ABB=ON  L43 AND (SUPPRESS? OR PREVENT?)/TI

     FILE 'CANCERLIT, MEDLINE' ENTERED AT 12:23:44 ON 10 MAY 2005
L46       201135 SEA ABB=ON  EPITHELIUM+NT/CT
L47        61044 SEA ABB=ON  OVARY+NT/CT
                D QUE L22
L48           30 SEA ABB=ON  L21 AND L17 AND (L18 OR L46)
L49        60745 SEA ABB=ON  (L18 OR L46)(L) DE/CT
L50           25 SEA ABB=ON  L21 AND L17 AND L49
                D QUE
L51        18069 SEA ABB=ON  L16(L)(PD OR AD OR TU OR PK)/CT
L52           25 SEA ABB=ON  L51 AND L17 AND L49
L53            0 SEA ABB=ON  L52 AND L47
L54            0 SEA ABB=ON  L51 AND (L18 OR L46) AND L17 AND L47
L55           22 SEA ABB=ON  L51/MAJ AND L17 AND L49
L56           15 DUP REM L55 (7 DUPLICATES REMOVED)
                     ANSWERS '1-7' FROM FILE CANCERLIT
                     ANSWERS '8-15' FROM FILE MEDLINE
                D TRIAL 1-5
L57            0 SEA ABB=ON  L51 AND L17 AND L47
                D QUE

     FILE 'DRUGU' ENTERED AT 12:30:52 ON 10 MAY 2005
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                E VITAMIN D+ALL/CT
                E VITAMIN-D+ALL/CT
                E E2+ALL
L58          6203 SEA ABB=ON  VITAMINS-D+NT/CT
                E APOPTOSIS/CT
L59         12638 SEA ABB=ON  APOPTOSIS/CT
                E EPITHELI/CT
L60           587 SEA ABB=ON  EPITHELIAL/CT OR EPITHELIAL-CELL/CT
                E EPITHELIUM/CT
L61          4742 SEA ABB=ON  EPITHELIUM/CT
L62             1 SEA ABB=ON  L58 AND L59 AND (L60 OR L61)
                D TRIAL
L63         25360 SEA ABB=ON  OVAR?
L64          8515 SEA ABB=ON  APOPTOSIS-INDUCER/CT
L65             1 SEA ABB=ON  L58 AND (L59 OR L64) AND (L60 OR L61)
L66             3 SEA ABB=ON  L58 AND (L59 OR L64) AND L63
                D TRIAL 1-3
L67         30748 SEA ABB=ON  VITAMINS/CC
L68             2 SEA ABB=ON  L58 AND (L59 OR L64) AND L63 AND L67

     FILE 'STNGUIDE' ENTERED AT 12:35:40 ON 10 MAY 2005

     FILE 'DRUGU' ENTERED AT 12:36:03 ON 10 MAY 2005
L69          1406 SEA ABB=ON  L5
                D QUE L65
                D QUE L68
L70             3 SEA ABB=ON  (L58 OR L69) AND (L59 OR L64) AND (((L60 OR L61))
                OR (L63 AND L67))

     FILE 'STNGUIDE' ENTERED AT 12:37:15 ON 10 MAY 2005

     FILE 'PASCAL, BIOTECHNO, BIOSIS, IPA, CONFSCI, DISSABS, TOXCENTER, WPIDS'
     ENTERED AT 12:41:34 ON 10 MAY 2005

     FILE 'STNGUIDE' ENTERED AT 12:44:06 ON 10 MAY 2005

     FILE 'PASCAL, BIOTECHNO, BIOSIS, IPA, CONFSCI, DISSABS, TOXCENTER, WPIDS'
     ENTERED AT 12:46:44 ON 10 MAY 2005
L71         83087 SEA ABB=ON  (HYDROXYVITAMIN OR DIHYDROXYVITAMIN OR VITAMIN)(W)(
                D OR D2 OR D3) OR CHOLECALCIFEROL# OR DIHYDROTACHYSTEROL# OR
                ERGOCALCIFEROL# OR ERGOSTEROL#
L72         13741 SEA ABB=ON  HYDROXYCHOLECALCIFEROL# OR CALCIFEDIOL# OR
                CALCITRIOL#
L73           330 SEA ABB=ON  (CHOLE OR ERGO)(W) CALCIFEROL# OR (DIHYDRO OR DI
                HYDRO)(W)(TACHYSTEROL# OR TACHY STEROL#)
L74         41391 SEA ABB=ON  L5
L75        554854 SEA ABB=ON  EPITHELI?
L76        294894 SEA ABB=ON  APOPTO?
L77        175236 SEA ABB=ON  CELL?(3A) DEATH
L78        362365 SEA ABB=ON  OVAR?
L79           145 SEA ABB=ON  (L71 OR L72 OR L73 OR L74) AND L75 AND (L76 OR
                L77)
L80            13 SEA ABB=ON  L79 AND L78
L81         38204 SEA ABB=ON  CHEMOPROPHYL? OR CHEMOPREVENT? OR CHEMO(W)(PROPHYL?
                 OR PREVENT?)
L82            28 SEA ABB=ON  L79 AND L81
L83            28 SEA ABB=ON  L82 NOT L80
L84            16 DUP REM L83 (12 DUPLICATES REMOVED)
                     ANSWERS '1-6' FROM FILE PASCAL
                     ANSWERS '7-8' FROM FILE BIOTECHNO
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                    ANSWERS '9-11' FROM FILE BIOSIS
                    ANSWERS '12-13' FROM FILE DISSABS
                    ANSWERS '14-16' FROM FILE TOXCENTER
               D SCAN

     FILE 'STNGUIDE' ENTERED AT 12:51:57 ON 10 MAY 2005

     FILE 'CAPLUS' ENTERED AT 12:53:30 ON 10 MAY 2005
               D QUE L14
               D QUE L45
L85          7 SEA ABB=ON  L14 OR L45

     FILE 'CANCERLIT, MEDLINE' ENTERED AT 12:53:32 ON 10 MAY 2005
               D QUE L55
               D QUE L57

     FILE 'EMBASE' ENTERED AT 12:53:32 ON 10 MAY 2005
               D QUE L31
               D QUE L35
               D QUE L42
L86         12 SEA ABB=ON  L31 OR L35 OR L42

     FILE 'DRUGU' ENTERED AT 12:53:34 ON 10 MAY 2005
               D QUE L70

     FILE 'PASCAL, BIOTECHNO, BIOSIS, IPA, CONFSCI, DISSABS, TOXCENTER, WPIDS'
     ENTERED AT 12:53:35 ON 10 MAY 2005
               D QUE L80
               D QUE L82
L87         41 SEA ABB=ON  L80 OR L82

     FILE 'STNGUIDE' ENTERED AT 12:53:48 ON 10 MAY 2005

     FILE 'CANCERLIT, MEDLINE, DRUGU, CAPLUS, EMBASE, PASCAL, BIOTECHNO,
     BIOSIS, DISSABS, TOXCENTER, WPIDS' ENTERED AT 12:55:37 ON 10 MAY 2005
L88         49 DUP REM L55 L70 L85 L86 L87 (36 DUPLICATES REMOVED)
                    ANSWERS '1-7' FROM FILE CANCERLIT
                    ANSWERS '8-15' FROM FILE MEDLINE
                    ANSWERS '16-18' FROM FILE DRUGU
                    ANSWERS '19-24' FROM FILE CAPLUS
                    ANSWERS '25-29' FROM FILE EMBASE
                    ANSWERS '30-36' FROM FILE PASCAL
                    ANSWER '37' FROM FILE BIOTECHNO
                    ANSWERS '38-43' FROM FILE BIOSIS
                    ANSWERS '44-45' FROM FILE DISSABS
                    ANSWERS '46-48' FROM FILE TOXCENTER
                    ANSWER '49' FROM FILE WPIDS
               D IALL 1-18
               D IBIB ED ABS HITRN 19-24
               D IALL 25-49

     FILE 'HOME' ENTERED AT 12:56:16 ON 10 MAY 2005


     FILE HOME

     FILE REGISTRY
     Property values tagged with IC are from the ZIC/VINITI data file
     provided by InfoChem.
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STRUCTURE FILE UPDATES: 9 MAY 2005 HIGHEST RN 850130-09-5
DICTIONARY FILE UPDATES: 9 MAY 2005 HIGHEST RN 850130-09-5

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

****
* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *
****

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

FILE CAPLUS

FILE COVERS 1907 - 10 May 2005 VOL 142 ISS 20
FILE LAST UPDATED: 9 May 2005 (20050509/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE CANCERLIT
FILE COVERS 1963 TO 15 Nov 2002 (20021115/ED)

On July 28, 2002, CANCERLIT was reloaded. See HELP RLOAD for details.

CANCERLIT thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2002 vocabulary. Enter HELP THESAURUS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE MEDLINE
FILE LAST UPDATED: 6 MAY 2005 (20050506/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

The MEDLINE reload for 2005 is now available. For details enter HELP RLOAD at an arrow promt (=>). See also:

http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE EMBASE
FILE COVERS 1974 TO 5 May 2005 (20050505/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE DRUGU
FILE LAST UPDATED: 9 MAY 2005 <20050509/UP>
>>> DERWENT DRUG FILE (SUBSCRIBER) <<<

>>> FILE COVERS 1983 TO DATE <<<
>>> THESAURUS AVAILABLE IN /CT <<<

FILE STNGUIDE
FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: May 6, 2005 (20050506/UP).

FILE PASCAL
FILE LAST UPDATED: 9 MAY 2005 <20050509/UP>
FILE COVERS 1977 TO DATE.

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION IS AVAILABLE IN THE BASIC INDEX (/BI) FIELD <<<

FILE BIOTECHNO
FILE LAST UPDATED: 7 JAN 2004 <20040107/UP>
FILE COVERS 1980 TO 2003.

>>> BIOTECHNO IS NO LONGER BEING UPDATED AS OF 2004 <<<

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION AVAILABLE IN /CT AND BASIC INDEX <<<

FILE BIOSIS
FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 4 May 2005 (20050504/ED)

FILE RELOADED: 19 October 2003.

FILE IPA
FILE COVERS 1970 TO 2 MAY 2005 (20050502/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE CONFSCI
FILE COVERS 1973 TO 18 Mar 2005 (20050318/ED)

FILE DISSABS
FILE COVERS 1861 TO 27 APR 2005 (20050427/ED)

FILE TOXCENTER

FILE COVERS 1907 TO 10 May 2005 (20050510/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TOXCENTER has been enhanced with new files segments and search fields. See HELP CONTENT for more information.

TOXCENTER thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary. See http://www.nlm.nih.gov/mesh/ and http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html for a description of changes.

FILE WPIDS
FILE LAST UPDATED: 6 MAY 2005 <20050506/UP>
MOST RECENT DERWENT UPDATE: 200529 <200529/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE, PLEASE VISIT:
http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE http://thomsonderwent.com/coverage/latestupdates/ <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER GUIDES, PLEASE VISIT:
http://thomsonderwent.com/support/userguides/ <<<

>>> NEW! FAST-ALERTING ACCESS TO NEWLY-PUBLISHED PATENT DOCUMENTATION NOW AVAILABLE IN DERWENT WORLD PATENTS INDEX FIRST VIEW - FILE WPIFV.
FOR FURTHER DETAILS: http://www.thomsonderwent.com/dwpifv <<<

>>> THE CPI AND EPI MANUAL CODES HAVE BEEN REVISED FROM UPDATE 200501.
PLEASE CHECK:
http://thomsonderwent.com/support/dwpiref/reftools/classification/code-rev
FOR DETAILS. <<<

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